PHYSIOLOGY OF THE KIDNEY

HOMER W. SMITH

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PORTER LECTURES
SERIES IX

STUDIES IN THE PHYSIOLOGY OF THE KIDNEY

BY

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INTRODUCTION

In 1918, Dr. J. L. Porter, a general practitioner of Paola, Kansas, bequeathed all of his property to the School of Medicine of the University of Kansas, providing for a scholarship and permitting the authorities to use the balance of the income for any purpose they deemed best.

It was decided to use this fund to defray the expenses of a series of lectures to be given by outstanding members of the medical profession. The first of these was delivered in April, 1930, by Dr. L. F. Barker; the second was given in October, 1930, by Dr. Joseph Collins; the third was given in March, 1933, by Dr. J. S. Horsley; the fourth in 1934, by Dr. Richard Scammon; the fifth by Dr. Edward A. Doisy, in 1935; the sixth by Dr. Jennings C. Litzenberg, in 1936; the seventh by Dr. Chevalier Jackson, in 1937; the eighth by Dr. William Boyd, in 1938; and the ninth series, delivered in 1939, follows.

FOREWORD

The clinical studies on normal and hypertensive subjects reported here have been conducted as a collaborative program of the Department of Medicine and the Department of Physiology of New York University College of Medicine.

The author is indebted to Dr. William Goldring, Dr. Herbert Chasis and Dr. Hilmert A. Ranges for the opportunity to describe unpublished observations.

STUDIES IN THE PHYSIOLOGY OF THE KIDNEY

NEWER METHODS OF STUDY OF RENAL FUNCTION IN MAN

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The physiology of the kidney is so richly charged with both intrinsic interest and far-reaching implications that a speaker in this field possessing, as I do, not only limited time for exposition but limited first-hand experience, must take careful precautions against exceeding either of these limitations. In weighing my responsibility as a recipient of this lectureship I have thought that the generosity and intent of its founder could be met by confining my discussion to a few topics, rather than by attempting an extended résumé of our knowledge of renal function as a whole.

This first lecture will deal primarily with the physiological basis of recently developed methods for examining the normal and diseased kidney. It is a truism that medicine, as all other sciences, moves forward just as rapidly as do its methods, and no apology is needed for devoting so much time to this phase of the subject. The methods to which I will refer are functional methods for measuring the rate of glomerular filtration, the renal blood flow, and the quantity of intact, active glomerular and tubular tissue. The application of these methods in the examination of the action of drugs and physiological agents on renal function will serve as a logical bridge to the subject of the possible rôle of the kidneys in hypertension, with which the last lecture will be chiefly concerned.

I think it may safely be assumed that you are thoroughly familiar with the basic principles of renal function, but we

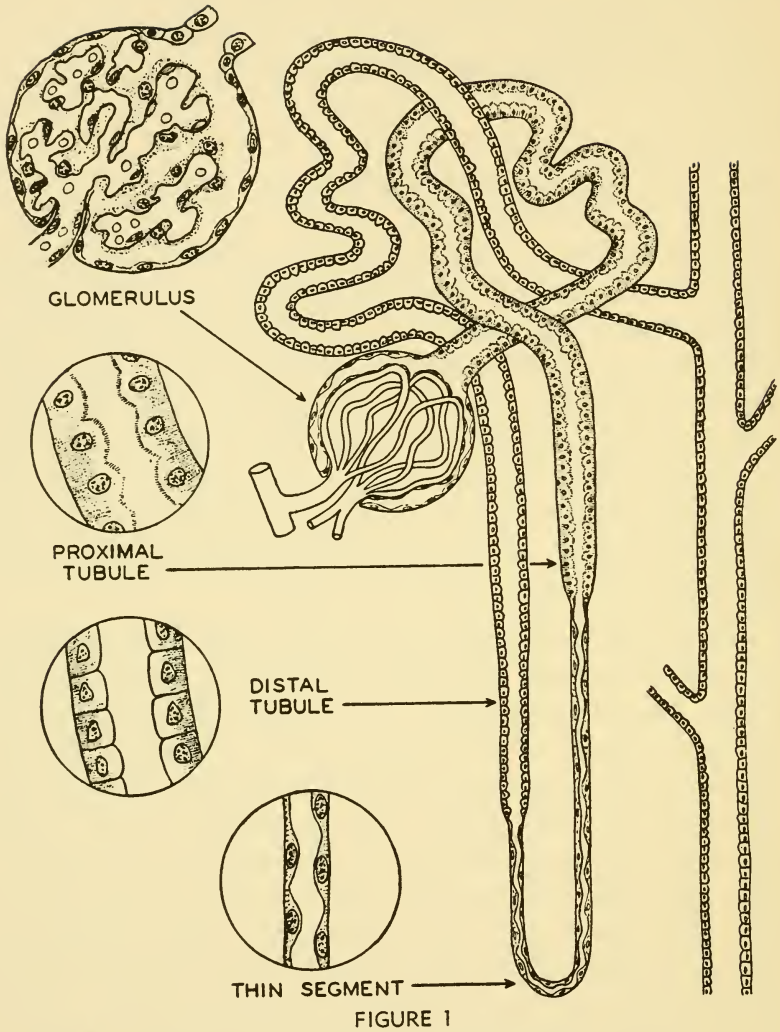

FIGURE 1. Diagrammatic representation of a human nephron. (From 45.)

may briefly review these principles in terms of a schematic human nephron. (Figure 1). This nephron consists of a glomerulus and a subjoined tubule, the latter being divided into three major segments: a "proximal" segment, which

immediately adjoins the glomerulus and has the largest diameter, and which is made up of irregular epithelial cells with brush-like striations at their internal border; an "intermediate" segment of smaller diameter, made up of quite flat or squamous cells; and a "distal" segment with fairly regular columnar epithelium having striations in the basal aspect of the cell, but lacking the brush formation in the internal border. The urine formed in this nephron is conducted to the renal pelvis by way of an arborized system of collecting tubules which appear to have no function other than that of conduits. According to Moritz and Hayman[24] there are an average of 1,283,000 such nephrons in each of the human kidneys.

The blood supply to this nephron consists of an afferent arteriole which breaks up immediately within the glomerulus to form an elaborate tuft of parallel capillaries; these capillaries converge into the efferent arteriole, which in turn subdivides again to form a secondary plexus of capillaries closely applied to the external or basement membrane of the tubule cells. Until recent years it was believed that all the blood reaching the tubules must first pass through the glomeruli, but the studies of MacNider,[20] Oliver[25] and Spanner[50] indicate that in the diseased kidney and possibly in the normal kidney as well, circulation in the peritubular capillaries may be established independently of the glomeruli by direct anastomoses between the arteriolar tree and either the capillary or venous channels. (See also 8).

Every student of renal physiology recalls Cushny's theory of urine formation. It was the cardinal premise of this theory that the formation of urine begins with the separation in the glomeruli of an ultrafiltrate identical in composition with the plasma except for the absence of the plasma proteins, to

which the glomerular capillaries were presumed to be impermeable. The actuality of this process of glomerular filtration is now established beyond the slightest doubt. The painstaking investigations of Professor Richards and his co-workers on the composition of the glomerular fluid in the frog and other cold-blooded animals, investigations begun in 1924 and only recently published in full,[29] have afforded incontrovertible proof of this thesis in these animals. Minute amounts of fluid have been collected from the glomerular capsule of Amphibia and reptiles by means of a Chamber's micro-dissection pipette, and by micro-analytical methods of high accuracy these minute quantities of fluid have been analyzed for various constituents. Comparison of the capsular fluid and of the plasma simultaneously circulating in the animal has demonstrated that fats and plasma proteins, or substances chemically combined with these large molecular aggregates, are the only important constitutents of the plasma that do not pass through this filtering bed. Since certain substances, such as glucose and chloride, are invariably present in the capsular fluid although they may be nearly or wholly absent from the urine, these investigations also afford a direct demonstration of the actuality of tubular reabsorption—which process is, of course, a corollary of glomerular filtration. By a still more admirable technique the Philadelphia investigators have been able to follow the processes of tubular reabsorption, and to demonstrate the specific role of the proximal and distal tubules in the reabsorption of various substances.

Because of the similar anatomy of the glomerulus in frog and man, the above evidence for glomerular filtration could by inference be transferred directly to the human kidney. Actually, inferential transfer is no longer necessary, for data are now available on the excretion of a variety of substances

in man which afford convincing evidence that a process of glomerular filtration, identical with that in the frog, occurs in man.

Those who recall the details of Cushny's theory will recollect that that writer was opposed to the belief that substances could be excreted directly by the tubule cells into the tubular urine without the interposition of the glomeruli. Cushny's opinion on this matter was, I believe, influenced by the conviction that such a process of tubular excretion must involve vital activity on the part of the tubule cells, a vital activity that transcended investigation and quantitation. In the previous century the doctrine of vitalism had been expelled from the physiology of nerve and muscle and, commendably, Cushny had no wish to see it regain a foothold in the physiology of the kidney. Subsequent investigations, however, have not only demonstrated that tubular excretion actually occurs, but they have shown that this tubular process, far from being vitalistically indeterminate, is amenable to orderly, quantitative description. Recalling the many years during which the very existence of tubular excretion was vigorously denied by adherents of the Cushny theory, we may note that so far as affording us information on critical aspects of renal activity, this process of tubular excretion is of much greater importance than is glomerular function.

The first convincing evidence of tubular excretion appears to have been adduced by Marshall and Vickers from a study of the excretion of phenol red in the dog, but the most emphatic evidence consists of observations of Marshall and Grafflin and of Edwards and Condorelli on the aglomerular fish kidney. For the details of investigations on the aglomerular kidney we may refer to the summaries of Marshall[21] and Shannon.[33] It will suffice to point out here that the

aglomerular tubule is capable of excreting all the more important constituents normally present in fish urine: magnesium, sulfate, chloride, potassium, ammonia, creatinine, creatine, uric acid, the foreign substances, iodides, nitrites, thiosulphates and sulphocyanates, and the dyes, indigocarmin, neutral red and phenol red. There has subsequently been added to this list the organic iodine compounds, diodrast and hippuran.[9] By another technique, utilizing in vitro cultures of kidney tissue, Chambers and Kempton[4] and Cameron and Chambers[3] have afforded a direct visual demonstration of tubular excretion in the mesonephric tubule of the chick and the metanephric tubule of man. Good evidence of the tubular excretion of urea in the frog has been advanced by Marshall[21] and independently by Höber.[14]

The data now available on man leave no doubt that tubular excretion plays a very important part in the excretion of phenol red,[11] diodrast and hippuran,[17, 47] iopax, neoiopax, skiodan[48] and creatinine,[34] but even prior to these demonstrations the possibility of tubular excretion in man had to be accepted on inference. Cytologically, the aglomerular tubule appears to be roughly homologous with the proximal segment of the human nephron and, without implying a perfect parallel in function, the demonstration that the aglomerular tubule can excrete a large variety of substances made it necessary to assume, in the absence of evidence to the contrary, that the human tubule might also be able to excrete them. Since, by the filtration-reabsorption mechanism of the nephron, the glomerular filtrate undergoes a variable degree of concentration by the reabsorption of water, it is impossible to determine directly from the composition of blood and urine whether the excretion of any one of several substances involves filtration alone, or filtration plus either tubular re-

absorption or tubular excretion. Once tubular excretion was admitted as a possibility, it was clear that the unravelling of the problems of renal function could not advance beyond the stage of speculation, whether nephrons were investigated individually or *en masse,* until there was available at least one substance which was known for certain to be neither excreted nor reabsorbed by the tubule cells. Once such a substance had been discovered, it could be used as a standard of reference with which to measure the tubular reabsorption of water, and hence to examine the mechanism of excretion of any other substance. Since this question cannot be answered in any instance by direct comparison of the absolute quantity of substance filtered with the quantity ultimately excreted, there remains as the only method of examination a comparison of the rates of excretion of various substances relative to their respective plasma concentrations.

It was with the recognition of these facts that observations on the relative rates of excretion of various substances in the dog were begun in my laboratory in 1929. We started from Marshall's[21] observation that the aglomerular kidney cannot under any circumstances excrete glucose; presumably the tubule cells have in their evolution never acquired the capacity to excrete this valuable foodstuff. But even assuming that the human tubule is also unable to excrete glucose, nevertheless this tubule is obviously able to reabsorb it, since glucose must be present in the glomerular filtrate although it is normally absent from the urine. Consequently we turned to the various non-metabolized carbohydrates, substances which are relatively inert and which are copiously excreted by the kidneys, as representing the type of compound most likely to fulfill the physiological specifications for measuring directly the degree of water reabsorption. Since it is inad-

visable to draw conclusions from a single species, these investigations, as indeed nearly all our investigations since, were extended to several species, principally the dogfish, the dog, and man. The dogfish was chosen because it is the lowest of the vertebrates which lends itself to experimental investigation; it has, moreover, certain unique features such as the capacity to actively conserve urea which make it a critical testing-ground for any theory. The dog kidney very closely resembles the human kidney in its functional capacities, and very accurate quantitative observations can be made upon trained, unanesthetized dogs. And in the last analysis every conclusion reached from a study of the lower animals must, of course, be put to its final test in man. In addition to these three species, numerous supplementary observations have been made by investigators in New York University College of Medicine on the sculpin, the chicken, the rabbit, the sheep, the seal, the monkey and the anthropoid apes (See 45). I feel that this wide foundation of comparative physiology is essential if we are to interpret with confidence details of function in the human kidney.

Among the first compounds with which we worked were xylose, sucrose and raffinose. Xylose and sucrose are not excreted by the aglomerular kidney, while in the dogfish, dog and man these three sugars show in simultaneous experiments almost identical concentration ratios (i.e., urine/plasma, or U/P ratios); i.e., they are concentrated in the tubule to the same extent.[43] From this fact we concluded that they are excreted by glomerular filtration without the participation of tubular excretion, and with negligible passive back-diffusion across the tubule. Subsequent investigations have substantiated both of these conclusions. From comparisons of the concentration ratios of the sugars with the concentration

ratio of urea before and after phlorizin (which drug blocks the reabsorption of glucose) it was concluded that the sugars are not actively reabsorbed by the tubules, as is glucose. On this point we were to prove ourselves in error, for urea, as we now know, is excreted in a variable manner and in it we chose an unreliable standard of reference. But since these carbohydrates consisted of small molecules which might escape from diseased tubules, or from normal tubules at very low urine flows, we sought further in the field of carbohydrates for a larger molecule, and this line of investigation led us to the use of inulin.

Inulin is a starch-like polysaccharide composed of 32 hexose molecules (mostly fructose) and having a molecular weight of 5200.[52] However, because of the elongate nature of the polysaccharide molecule, its diffusion coefficient is considerably less than would be expected from its molecular size, being only twice as great as hemoglobin.[2] It is completely filterable from plasma through collodion membranes, but it is about as large a molecule as one would expect to filter through the glomeruli. It is physiologically inert and rapidly and quantitatively excreted in the urine.

Our first comparisons of the excretion of xylose and inulin revealed that our conclusion that there was no active reabsorption of the sugar was wrong, the concentration ratio of xylose being consistently about 20 to 25 per cent lower than the simultaneous concentration ratio of inulin in the dogfish,[34] sculpin (Clarke, unpublished), dog, sheep, and man.[44] Unless one postulates the tubular excretion of inulin in the face of much evidence arguing against it, this means that a quarter of the filtered xylose is reabsorbed by the tubule. But if an inert sugar, such as xylose or sucrose, can be actively reabsorbed by the tubules, how can one exclude the

possibility of some, even if slight, tubular reabsorption of inulin, which is a carbohydrate, even if a large and very inert one? This question was answered in the dog by Shannon,[35, 36] who showed that inulin and creatinine are concentrated to precisely the same degree. Similar identity in the concentration ratios of creatinine and inulin has been demonstrated in the rabbit,[16] the seal,[44] the sheep[37] and, as Forster has recently shown, in the frog.[10] Since it is implausible that two substances of such different natures as inulin and creatinine should be either excreted or reabsorbed by the tubules to precisely the same extent in these different species of animals, it may be accepted that in these species both substances are excreted by filtration without tubular participation.

But the concentration ratio of creatinine is very much higher than that of inulin in the dogfish,[53] the red grouper,[26] the chicken,[38] and the anthropoid apes.[46] This discrepancy is also evident in man; when creatinine is freshly injected into the blood it is concentrated by the human kidney about 40 per cent more than is inulin;[19, 22, 34] here either 40 per cent of the inulin is reabsorbed, or considerable creatinine is excreted by the tubules in addition to that which is filtered. This is an important question since, on the basis of Rehberg's[28] early investigations, the creatinine clearance is widely accepted as a measure of the rate of filtration in man. The difference between the creatinine and inulin clearances may be as much as 70 per cent. Shannon[34] in his original study on man decided that creatinine was excreted in part by the tubules. Though I feel that the evidence on this point, when considered critically, is conclusive, this evidence has not been such as to convince all investigators and we have never abandoned our efforts to reinforce it. It is gratifying that we are able to add supplementary facts at this time.

Independently of our own investigations with inulin in a variety of species, Richards and his co-workers, led by the same considerations as ourselves, were examining the excretion of this substance in the frog, Necturus and the dog. Hendrix, Westfall and Richards[13] showed that it is completely filterable through the glomeruli of the frog and Necturus. A preliminary report of Richards, Westfall and Bott[31] indicated considerable discrepancy in the way inulin and creatinine are excreted in the dog, but reinvestigation with improved analytical procedures[32] removed these discrepancies, so that these investigators as well as Van Slyke, Hiller and Miller[51] are now in agreement with Shannon's[35,36] observations that in the dog these two substances have identical concentration ratios within the limits of analytical error. More recently, Richards, Bott and Westfall[30] have added to the evidence against tubular excretion of inulin in the frog, rabbit and dog by perfusing the kidneys of these animals with blood at pressures too low to permit glomerular filtration to occur. Under these conditions hippuran and phenol red, which are indubitably excreted by tubules, accumulate in the tubular urine whereas inulin and creatinine do not.

Deferring for a moment a further discussion of the excretion of inulin in man, we will tentatively assume that this polysaccharide is filterable through the glomeruli in the same concentration per unit of water as it is present in the plasma; thereafter it passes down the tubules like a stream of inert marbles, the filtered quantity suffering neither increase nor decrease in consequence of tubular excretion or tubular reabsorption. It follows that the degree of water reabsorption is revealed by the inulin urine/plasma (U/P) ratio, and also that the rate of glomerular filtration is given by the quantity of inulin excreted per minute (UV) divided by the concen-

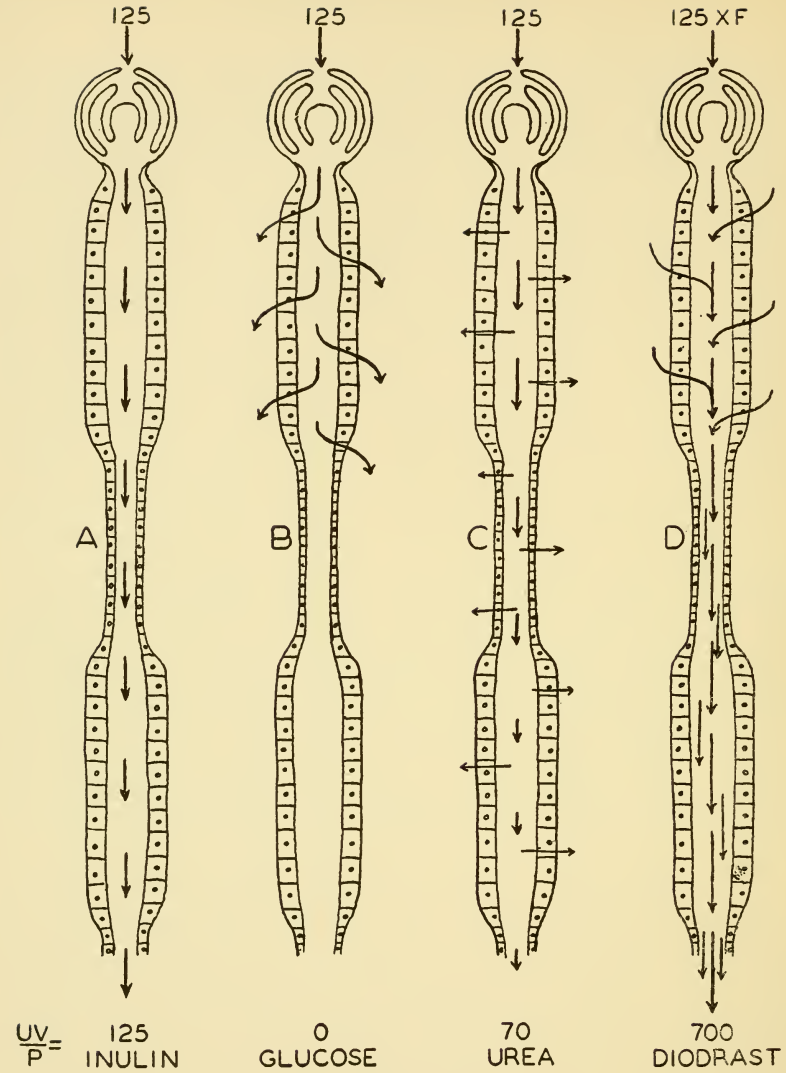

FIGURE 2

FIGURE 2. Scheme to illustrate the excretion of (A) inulin, which is excreted solely by filtration with no tubular reabsorption; (B) glucose, which is filtered, but at normal plasma level and rate of filtration is completely reabsorbed by the tubule; (C) urea, which is filtered, but in part escapes from the tubular urine by diffusion; (D) diodrast, which is excreted both by filtration and tubular excretion. UV/P is the clearance in each instance, i.e., the virtual volume of blood cleared per minute. (U and P are the concentrations per unit volume of urine and plasma, and V is urine flow per minute.) The inulin clearance is taken as equal to the rate of filtration of plasma. F is the per cent of diodrast filtrable from the plasma, 1.00-F being the per cent bound to plasma proteins.

tration in each cc. of plasma (P). (See Figure 2a). The filtration rate in man, measured in this manner, averages about 125 cc. per minute.[47] This figure is not surprisingly large when we consider that the total surface area of the glomerular capillary bed, as calculated from Book's[1] data on a typical glomerulus, is nearly 1.0 square meter. Out of this 125 cc. of water filtered through the glomerulus, 124 cc. are on the average reabsorbed by the tubules, leaving only 1 cc. to be excreted in the urine. In consequence of the variable reabsorption of water, inulin (and of course other substances) appears in the urine in variable concentrations, but variations in urine flow or the degree of urine concentration do not normally entail any change in the rate of filtration itself.[7]

Returning to the overall operation of the kidney, we may say that it is the function of this organ to clear the blood flowing through it of various substances, and that the overall efficiency of this clearance process in any instance depends upon the specific mechanism of exretion, which in turn will depend upon the properties of the substance under examination.

Rewording the above discussion, we may say that inulin is cleared from the plasma exclusively by a process of filtration, unmodified by tubular reabsorption or tubular excretion. Hence the volume of plasma cleared of inulin in each minute's time must be equal to the rate of filtration itself.

To extend this idea to other substances, we may say that glucose (Figure 2b) is initially cleared from the plasma by filtration at a rate identical with that of inulin, but because all the glucose is normally actively reabsorbed by the tubules the volume of plasma which is cleared of glucose per minute's time in the overall operation is zero. Urea (Figure 2c) is likewise initially cleared from the plasma at a rate identical

with that of inulin, but about 50 per cent of this filtered urea escapes from the tubular urine by passive diffusion and consequently only half as much plasma is actually cleared of urea as is cleared of inulin. Diodrast (Figure 2d) is cleared from the blood both by filtration and tubular excretion, and hence a much larger volume of plasma is cleared of this substance per minute than could be cleared by filtration alone.

Thus we may legitimately speak of the inulin "clearance" (=filtration rate) the glucose "clearance", the urea "clearance" and the diodrast "clearance", as the virtual volume of plasma which is cleared of these particular substances in one minute's time. This virtual volume is quite simply calculated by dividing the quantity of substance excreted in one minute's time (UV) by the quantity contained in each cc. of plasma.*

I have made this perhaps unnecessarily slow approach to the concept of clearance, because it has been my experience that as soon as the word is mentioned, there may occur one of two adverse reactions: the auditor may infer that a clearance is just another empirical renal function test, of which there have been plenty in the history of renal physiology; or, discovering that a "clearance" involves an arithmetical calculation based upon concentrations in blood and the rate of excretion, he may shy away into the conclusion that it is incomprehensible to the non-mathematically minded. Neither inference is correct; the mathematics involved is but simple arithmetic, and the calculation is the only physiological and logical method of evaluating the over-all efficiency of the

*Since most of the substances with which we are concerned do not penetrate the red cells but are carried to the kidneys solely by the plasma, it is desirable, in order to avoid errors due to variable hematocrit, to make all clearance calculations on the basis of the concentration of substance in plasma rather than whole blood, and to call such clearance, "plasma clearance."

kidney in clearing the blood of any particular substance. One point which perhaps adds confusion to the notion of renal clearances in the minds of many is this: the word "clearance" was introduced into renal physiology in 1928 by Möller, Mackintosh and Van Slyke[23] as an empirical means of describing the excretion of urea, which is dependent upon the rate of urine flow. Variations in urine flow arise from variations in the amount of water which is reabsorbed from the glomerular filtrate by the tubules, and in consequence of the variable degree of concentration of the urea in the tubular urine a variable quantity of the filtered urea diffuses back across the tubules. But this is not true of inulin nor of other substances with which we will be concerned here; we may therefore divorce the concept of renal clearance from all association with urine volume *per se* and re-define it in the above general terms. Such a generalization of the concept of renal clearance was implicitly effected in 1932 by Jolliffe, Shannon and Smith[15, 43] in our description of the rate of excretion of various non-metabolized sugars by the dog, and it has proved to be a surprising fluid and useful mode of expression.

Let us now examine the clearance values of various substances in normal man, these clearances being measured when the substances are present in the plasma at suitably low concentrations, as shown at the left of Figure 3. These clearances vary upwards from 0.0 to slightly above 700 cc. of plasma per minute. The glucose clearance, of course, is zero because at normal plasma levels the filtered glucose is all reabsorbed by the tubules. The same may be said of vitamin C, and the various other substances not shown in the figure, such as amino acids, uric acid, sodium, potassium, chloride and SO_4; all of these substances have been demonstrated to be

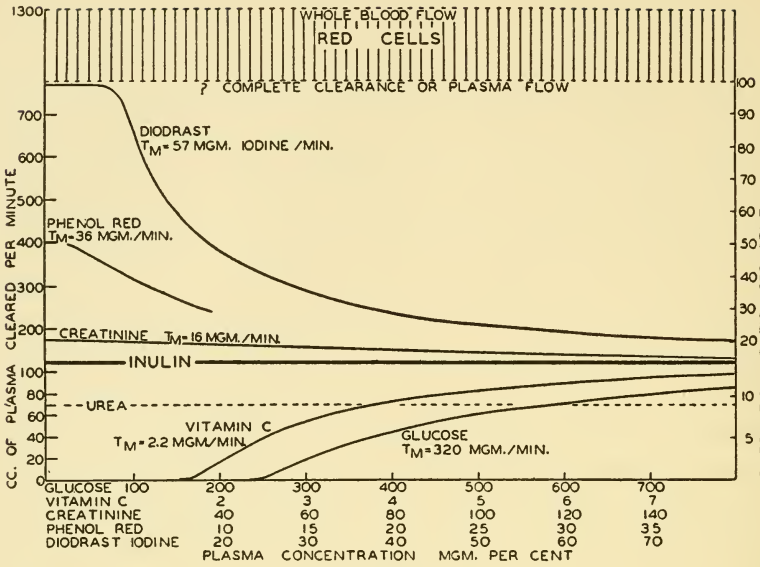

FIGURE 3

FIGURE 3. Diagrammatic summary of excretion of various types of compounds by the human kidney. The quantitative relations are fully described in the text.

completely filterable from plasma, and their low clearances must be attributed to tubular reabsorption. The urea clearance (plasma) averages about 70 cc., inulin, 125 cc., creatinine, 175 cc., phenol red, 400 cc., and diodrast, 737 cc. per minute. From what has been said above, we may infer that the various values of these clearances reveal differences in the efficiency with which the respective substances are excreted, these differences being due to differences in the mechanism of excretion. Accepting the presumption that the inulin clearance is equal to the rate of glomerular filtration, it follows that substances, such as Na, K, Cl, amino acids, glucose and vitamin C, the clearances of which are less than the inulin clearance, must be reabsorbed by the tubules (providing of course that they are filterable through the glomeruli), while substances such as creatinine, phenol red, iopax, hippuran and

diodrast, the clearances of which are greater than the inulin clearance, must be excreted by the tubules in addition to being filtered through the glomeruli.

I have chosen to present a comprehensive picture of renal function in one diagram because it enables us to grasp quickly certain fundamental principles. We can discover important facts about these processes of tubular absorption and excretion by observing what happens to these several clearances when the plasma concentration is changed. Changing the plasma concentration of inulin has no effect on the inulin clearance, since whatever inulin is present in the glomerular filtrate is passed on into the urine regardless of whether it is a large or small amount. The same may be said of urea; the urea clearance is less than the inulin clearance because of diffusion out of the tubules rather than because of active reabsorption, and this process of diffusion is determined by the rate of urine flow rather than by the concentration of urea in the tubular urine or the blood.

But in the case of those substances which are actively reabsorbed or excreted by the tubules, any change in plasma concentration beyond a critical level influences the clearance in a definite, reproducible manner. This dependence on the concentration term arises from the fact that in the operations of reabsorption and excretion the tubule cells can handle only certain limited quantities of any substance per unit time; i.e., these cellular operations are readily loaded to the saturation point. For example, the tubule cells cannot reabsorb an infinite amount of glucose per unit time; as the plasma concentration of glucose is increased the concentration of glucose in the glomerular filtrate is increased *pari passu*, and therefore more glucose presented to the tubules per minute, and ultimately there comes a time when the tubules are loaded

to capacity and some glucose escapes reabsorption and is excreted in the urine. A careful analysis of this phenomenon in the dog has been made by Shannon and Fisher,[41] and it has been found that the tubules are capable of reabsorbing all the glucose from the glomerular filtrate up to a point where this reabsorption reaches a certain maximal rate, in milligrams of glucose per minute. For brevity we may designate this maximal rate of tubular reabsorption of glucose as glucose-Tm. Recent (unpublished) observations on man indicate that here precisely the same type of limitation applies; the maximal rate of tubular reabsorption of glucose in man typically ranges around 350 mgm. per minute. This figure is easily determined by raising the plasma glucose to a high level, and measuring the simultaneous rate of filtration and of glucose excretion. The curve in Figure 3 represents the glucose clearance in an individual whose filtration rate (inulin clearance) is taken to be 125 c.c. per minute, whose maximal rate of tubular reabsorption of glucose (glucose Tm) is taken to be 320 mgm. per minute, and in whom the plasma level of glucose has been raised from 200 to 800 mgm. per cent. At 256 mgm. per cent of glucose in the plasma the rate of filtration of glucose ($125 \times 256/100$ or 320 mgm. of glucose per minute) is just equal to the maximal rate of reabsorption; at plasma levels above this all excess glucose is excreted in the urine, so that the glucose clearance now rises and approaches the inulin clearance asymptotically. Thus the physiological basis of the glucose threshold consists of a constant maximal rate of tubular reabsorption combined with a variable rate of glomerular filtration and of course a variable concentration of glucose in the plasma and therefore in the glomerular filtrate.

Ralli, Friedman and Rubin[27] have recently shown that

vitamin C is handled by the human kidney in a manner similar to glucose; the maximal rate of tubular reabsorption averages 2.2 mgm. per minute, which figure we have used in the chart; at an average filtration rate of 125 cc. per minute, vitamin C will first appear in the urine at 1.76 mgm. per cent, and at increasing plasma levels the vitamin C clearance will increase and approach the inulin clearance asymptotically, as in the case of glucose.

Goudsmit, Power and Bollman[12] have recently reported that SO_4 is handled in a somewhat similar manner by the tubules of dog and man, but too little information is available on the reabsorption of Na, K, Cl, amino acids, uric acid, etc., to say whether these substances will show a maximal rate of tubular reabsorption or not. It would be naive to suppose that all reabsorptive mechanisms in the kidney were as simple as this, and indeed it cannot as yet be said why a maximal rate of reabsorption should limit the reabsorption of glucose or vitamin C.

Turning now to the process of tubular excretion, the fact that creatinine, phenol red, diodrast and other substances are excreted by the tubules does not exclude the fact that they are also excreted by glomerular filtration. They are excreted through the glomeruli insofar as they are present in the plasma in a filterable form. The creatinine clearance, for example, has a value of about 40 per cent greater than the inulin clearance; since creatinine is completely filterable from the plasma, this means that in addition to 125 cc. of plasma per minute which are cleared of creatinine by filtration, an additional 50 cc. per minute are cleared by tubular excretion. Raising the plasma level of creatinine will not affect the filtration clearance, but it will affect the tubular clearance, for again there is a maximal quantity of creatinine which can

be handled by the tubule cells per unit time. The net consequence of this circumstance is that at high plasma levels of creatinine the total creatinine clearance is depressed towards the level of the inulin clearance (see 40). The same may be said of the excretion of phenol red[40] and diodrast, hippuran and iopax, which have been examined by other investigators.[47,48] In every instance where an adequate examination has been possible, it has been shown that, just as in the case of tubular reabsorption, so in tubular excretion there exists a limitation in tubular activity, which takes the form of a maximal rate of excretion.* When the plasma concentration of any of these substances is raised above a critical level the tubular mechanism becomes saturated, so to speak, and excretes the substance at a maximal rate. This maximal rate has, of course, a different value for each substance. Again we may designate the maximal rate by Tm, and speak of the creatinine Tm and phenol red Tm, diodrast Tm, etc., and these values will of course differ in different individuals, depending upon the size of the kidneys or the number of normal nephrons. The maximal rate of tubular excretion may be determined by deducting the quantity filtered through the glomeruli from the total quantity excreted per minute, when the plasma level has been raised to such a level as to load the tubule cells to full capacity. The curves shown in Figure 3 relating the creatinine, phenol red and diodrast clearances to plasma concentration, are calculated on the basis of average observed Tm values in normal man.

This diagram serves not only to illustrate certain prin-

*The glomerular excretion of all these substances, with the exception of creatinine, is complicated by the circumstance that they are in part bound to plasma proteins in apparently all species and are not completely filterable. Data are available for correcting for this protein binding, although we need not detail these corrections here (45,49).

ciples of renal function, but it focusses attention again on the importance of accurately measuring the rate of glomerular filtration, for all subordinate calculations of what is going on in the tubules in health or disease depend upon the accuracy of this measurement. For this reason I would like to return for a moment to the discussion of the inulin clearance. I have spoken of our continued efforts to obtain further evidence on the mechanism of the excretion of inulin. The difficulties in this problem lie in obtaining substances for which accurate methods of analysis in blood and urine are available, and in the selection of substances which have suitable physiological properties. The field is narrowed by the fact that the renal tubules are known to reabsorb or excrete so many different types of compounds. Strong electrolytes are handled by the tubules in a complex manner, and many weak electrolytes (uric acid, creatinine, amino acids, etc.) presumably become entangled in these tubular processes or are themselves handled by specific reactions. Even though a weak electrolyte might escape tubular reabsorption or excretion in the normal kidney, or under special circumstances, there is no assurance that it would remain inviolable under all circumstances, or in the nephron with perturbed function. In our further search, therefore, we have concentrated upon substances which have as little chemical reactivity as possible, for in theory we would like a molecule that was absolutely chemically inert, and one endowed with such physical properties that it would not diffuse through a normal or even a moderately injured cell. We have recently had under examination the polyhydric alcohols, sorbitol and mannitol, in the belief that these represent a step in the right direction. Dr. W. W. Smith has recently devised methods for the analysis of such compounds in blood and urine, and in a limited

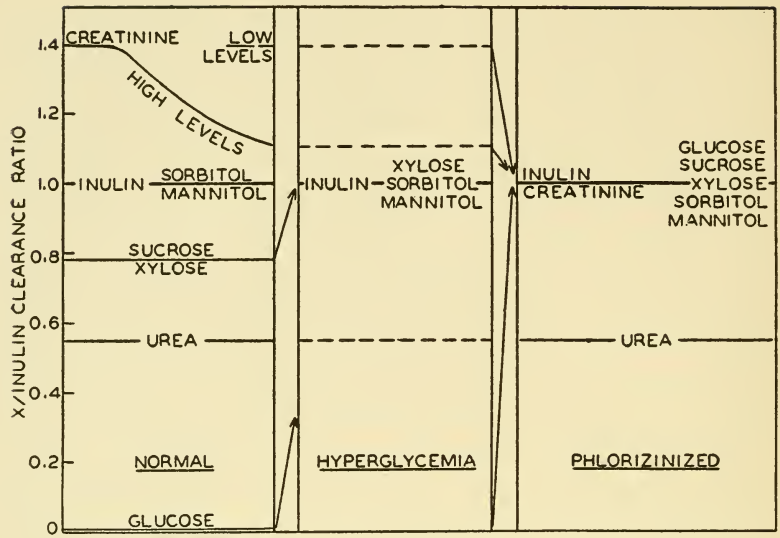

FIGURE 4

FIGURE 4. Diagrammatic summary of the present evidence, based on clearance ratios, indicating that the inulin clearance is at the level of glomerular filtration in man.

series of studies with these hexahydric alcohols we find that their concentration ratios, and therefore their renal clearances, in both dog and man are identical with the inulin clearance with a standard deviation of about 4 per cent. These observations are summarized in Figure 4. Though sorbitol and mannitol are similar to glucose in that they contain a number of hydroxyl groups, the absence of either a free aldehyde or ketone group, as in the sugars, argues tentatively against their being actively reabsorbed by the mechanism that reabsorbes glucose, and the identity of the three clearances is, I believe, good evidence that all three substances are excreted by filtration without tubular reabsorption.

To bring all the evidence together I would briefly note a few additional facts. Shannon has recently shown that in the dog[39] and man (unpublished) during hyperglycemia, when

the glucose reabsorptive mechanism is loaded to capacity, xylose is excluded from tubular reabsorption, and the xylose clearance rises to identity with the inulin clearance. (The behavior of sucrose and raffinose under these conditions has not been examined.) Consequently, as illustrated in figure 4, during hyperglycemia we may equate the clearances of xylose, mannitol, sorbitol and inulin.

It has long been known that the drug phlorizin induces glycosuria at all plasma levels, and in our first studies we attributed this to the blocking of the reabsorption of glucose in the tubules.[15] When phlorizin is administered to dog or man the process of sugar reabsorption by the tubules is completely abolished so that not only the glucose but also the xylose and sucrose clearances are nearly or quite identical with the inulin clearance,[5,42] and prior to direct examination, we may anticipate that after phlorizin this identity will include sorbitol and mannitol.

Concerning the excretion of exogenous creatinine in man there is not, in my opinion, the slightest doubt of Shannon's[34] original evidence in favor of tubular participation. And at high plasma levels of creatinine, the creatinine clearance approaches to within a few per cent of the inulin clearance, and this fact itself was advanced by Shannon to support the belief that the inulin clearance was at the level of filtration. On the other side, Ralli, Friedman and Rubin's[27] demonstration that the vitamin C clearance rises from zero and approaches to within 10 per cent of the inulin clearance at high vitamin C levels is additional evidence in this direction.

Phlorizin depresses the tubular excretion of creatinine in lower animals where this process is highly developed;[45] and in man it entirely abolishes the normal difference between the creatinine and inulin clearances, a result which, in view of

the above evidence, we must attribute to the depression of tubular activity.

These facts reaffirm my conviction that the inulin clearance is at the level of glomerular filtration in the human kidney. It is, however, highly desirable if possible to obtain some substance which has no chemical similarity to the carbohydrates, and which will add to or amend the above evidence, and this search will not be abandoned.

Returning now to the process of tubular excretion (Figure 3) it will be observed that the blood is cleared of substances such as phenol red and diodrast most efficiently at low levels, where the tubules are not loaded to capacity. It is also evident that diodrast is cleared more efficiently than is phenol red. Considered physiologically, there must be an upper limit to the possible range of clearance values, for the kidneys cannot excrete more of any substance per unit time than is carried to them by the blood in that interval:* that is, the upper limit of renal clearance values will be that of a substance which is completely cleared from the blood, and this clearance will be identical with the rate at which plasma itself is circulated through the kidneys.[11]

This can be made clear by a simple example: if X is a substance which is completely cleared from the renal plasma in a single circulation through the kidneys, and if each cc. of arterial plasma (=systemic venous plasma) contains 1 mgm. of X and if 700 mgm. of X are being concurrently excreted in the urine each minute, it follows that 700 cc. of plasma, no more and no less, must be flowing through the kidneys in each minute's time. It is the simple problem of how many

*Excluding, of course, storage or synthesis in the renal parenchyma. Synthesis of phenol red, diodrast, etc. is clearly excluded, and storage of these compounds under standard conditions has been ruled out by Smith, Goldring and Chasis (47).

cc. of plasma are required to deliver 700 mgm. of X per minute, if each cc. of plasma carries 1 mgm.

The determination of the extent to which the clearance of any substance approaches completeness (i.e., 100 per cent extraction, as shown at the right of figure 3) can only be answered at the present time by direct comparison of blood from the renal artery and the renal vein; and these blood samples must be collected under such conditions that renal function is not seriously disturbed. Since anesthesia and handling of the kidney do disturb renal function, this has proved to be a difficult undertaking in man, but we hope ultimately to make such determinations under entirely satisfactory conditions. However, the plasma diodrast clearance in normal man under basal conditions averages about 740 cc. per minute, which corresponds to slightly under 1300 cc. of whole blood.[47] The basal cardiac output we may take to be 4000 cc. per minute. In short, the renal blood flow as given by the diodrast clearance constitutes almost one third of the total cardiac output, and we infer that the actual total renal blood flow cannot be much in excess of this. There are other indirect considerations which need not be detailed but which indicate that the diodrast clearance is essentially a complete one, and until further information is available we may assume that such is the case.

We have, then, in the plasma diodrast clearance at low plasma levels of diodrast, a measure of the physiologically effective renal plasma flow in cc. per minute.* It is only necessary to divide the renal plasma flow by the per cent of plasma in whole blood to obtain the renal blood flow.

*This measurement is valid only so long as we do nothing to the kidney to change the extraction ratio of diodrast, i.e., so long as we do not impair the process of tubular excretion. Reasons have been given for believing that a change in extraction ratio can be detected by a change in the phenol red/diodrast clearance ratio (47).

By dividing the filtration rate (=inulin clearance) by the renal plasma flow (=diodrast clearance) we can calculate the fraction of the plasma which is filtered through the glomeruli. This filtration fraction will depend upon systemic blood pressure, the state of constriction or dilatation of the glomerular arterioles, the permeability of the glomerular capillaries, the intrarenal or capsular pressure, perhaps upon the time of contact of the blood with the glomerular capillaries, and possibly upon other factors. By following the filtration fraction under a variety of conditions we can learn much about the activity of the glomerular apparatus.

It will be convenient at this point to relate these quantitative methods to the architecture of the kidney, as illustrated in Figure 5. It will be recalled that in each kidney there are over a million nephrons, each of which is capable in

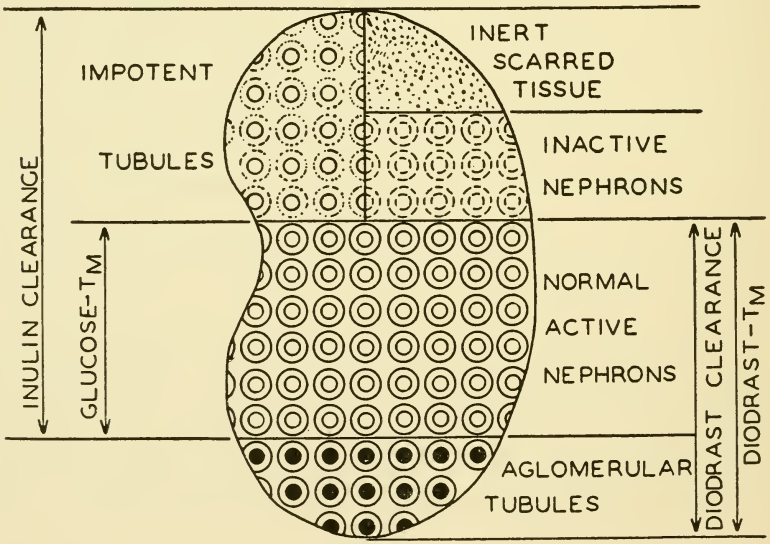

FIGURE 5

FIGURE 5. Functional types of nephrons to be expected in the normal and diseased kidney.

theory of functioning more or less independently. We may assume *a priori* that the blood flow to any nephron can be varied by physiological means, and that at a given blood flow the quantity of filtrate separated at the glomerulus can be varied by local changes in intraglomerular pressure, due, among other things, to changes in afferent and efferent arteriolar tone. It is conceivable that a glomerulus may be completely cut out of the circulation by local vasoconstriction, while the appended tubule continues to function in various excretory operations in the manner of the normal aglomerular nephron; or that blood can be shunted away from both glomerulus and tubule, rendering the entire nephron inactive. And conceivably the destruction of glomeruli or tubules may be effected separately during the course of disease.

It will simplify our subsequent discussion if we define in terms of the physiology of the individual nephron the chief deviations from normal function which may be expected to occur.

1. We will designate as *normal active nephrons* those nephrons which possess both normal glomeruli and tubules.

2. The term, *aglomerular tubules* may be used to designate nephrons of which the glomeruli have ceased to function for any reason, but in which the tubule is functionally intact and receiving an adequate supply of blood, and is capable of carrying on excretory operations.

3. Any nephrons which, though potentially capable of normal function, are excluded from function by ischemia we will designate simply as *inactive nephrons.*

4. The terms *impotent tubules* we can apply to nephrons in which the glomerulus remains intact and active, but the

tubule, by virtue of ischemia or local intracellular damage, is incapable of function. This category would include only patent nephrons which are connected with the collecting ducts and which therefore serve as passive conduits to drain glomerular filtrate out of the body.

5. In the category of *inert scarred tissue* we would include not only fibrotic glomeruli and fragmented or necrotic tubular tissue, but also anatomically intact nephrons which are obstructed by casts of epithelium, albumin, etc., or which are disconnected from the collecting ducts, so that function is at least temporarily impossible.

In the above schema the nephron is viewed as a unitary structure with but a single function. This is of course not true; the proximal tubule is probably concerned with the reabsorption of sodium, chloride, glucose, vitamin C and possibly other constituents of the glomerular filtrate, and with the excretion of creatinine, phenol red, diodrast and possibly other substances. The thin segment is perhaps chiefly concerned with the hypertonic reabsorption of water, the distal segment with the final adjustment of the urine in respect to chloride, pH, HCO_3, etc. But obviously we cannot appraise all these functional activities at this time. Our methods limit our examination to glomerular function, on the one hand, and on the other to two functions of the proximal tubule: the excretion of diodrast and the reabsorption of glucose.

A priori it may be supposed that even in the healthy kidney the number of normal active nephrons may be variable, giving way to either inactive nephrons or aglomerular nephrons; and with greater confidence we can expect to discover such transitions to occur in consequence of disease.

Utilizing the methods I have discussed above, we can

evaluate the number of normal active nephrons by glucose-Tm, since the maximal quantity of glucose in mgm. per minute which the kidneys will absorb is determined by the number of nephrons which are both receiving glomerular filtrate and capable of reabsorbing glucose from this filtrate. If the glomerulus of a particular nephron closes, converting it to an aglomerular tubule, or if the tubule itself is rendered inactive by ischemia, it will cease to contribute to glucose-Tm, and this figure will be decreased accordingly. Glucose-Tm will also be decreased by destruction of the reabsorption capacity of the tubule, even though the glomeruli remain open; in this case the nephron enters that category which we have called impotent. Though it is impossible at the moment to distinguish in the diseased kidney which of these three causes —glomerular ischemia, tubular ischemia or tubular injury —may be responsible for reducing glucose-Tm in the diseased kidney, this measurement can be used to determine whether the number of active normal nephrons in the kidney of a particular individual can be increased or decreased by any method.

Diodrast-Tm serves to measure the number of active excretory tubules, whether glomerular or aglomerular; it affords therefore a measurement of the total quantity of intact, tubular excretory tissue in the kidney, which may be designated as the tubular excretory mass.[47] We infer that this tubular excretory mass is identical with the quantity of physiologically intact proximal tubular tissue, since the evidence indicates that it is only by the proximal tubule that diodrast is excreted. Within wide limits both glucose-Tm and diodrast-Tm will, under appropriate plasma concentrations of glucose and diodrast, be independent of the rate of filtration or the rate of blood flow. That is, they afford us

absolute standards of reference of the mass of functioning tissue.*

Except insofar as glucose reabsorption and diodrast excretion may be separately impaired by disease, the relative values of glucose-Tm and diodrast-Tm, as compared with the normal ratio, will afford an indication of the presence and approximate number of aglomerular nephrons in the kidney.

Glomerular filtration can occur in both normal active nephrons and in the glomeruli of impotent tubules (which by definition are still connected with functional glomeruli); again the fraction of the glomerular filtrate furnished by these two adjacent categories cannot be distinguished directly, but it should ultimately be possible to reach a separate evaluation of the number of impotent tubules on the basis of the relative values of the filtration rate and glucose-Tm or diodrast-Tm.

Inactive tubules will be revealed only indirectly by an increase in diodrast-Tm under experimental or therapeutic conditions which abolish tubular ischemia, just as inactive glomeruli will be revealed only indirectly by an increase in glucose-Tm under conditions whereby glomerular ischemia is abolished.

*Short of complete cessation of filtration, the degree of reduction in filtration rate necessary to cause an individual nephron to drop out of glucose-Tm will be determined by the plasma level of glucose, which fact must be taken into account in the definition of "normal active nephrons".

Similarly, the degree of reduction in blood flow necessary to cause an individual nephron to drop out of diodrast-Tm will be determined by the plasma level of diodrast, which fact must be taken into account in the definition of the tubular excretory mass.

The diodrast clearance affords no information on the blood flow to either impotent tubules or scar tissue, but only to intact tubular tissue (the tubular excretory mass); hence it is appropriate for purposes of physiological comparison to relate the diodrast clearance to diodrast-Tm.

A reduction in diodrast clearance may be due to an actual reduction in blood flow, or to a decrease in extraction ratio, due to a reduction for any reason in the excretory capacity of the tubule. If the latter is due to disease the tubule would enter the category of impotent tubules or scar tissue.

Inert scarred tissue can be evaluated only by presumption when glucose or diodrast Tm are decreased below standard normal values.

The above synopsis, though in a sense theoretical and ahead of our factual knowledge of renal pathology, will serve to guide us in respect to what we should look for in the examination of the normal or diseased kidney.

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STUDIES IN THE PHYSIOLOGY OF THE KIDNEY

THE EVOLUTION OF THE KIDNEY

THE EVOLUTION OF THE KIDNEY*

Seventy-odd years have elapsed since Claude Bernard first apprehended the fact that the true medium in which we live is neither air nor water, but the blood, the internal medium, that bathes our muscles, glands and brain. This internal environment, as he called it, is a cosmos elaborately isolated from the external world and protected by a variety of physiological devices to the end that its composition shall remain unaffected by the sudden and sometimes severe changes that beset the other and unstable cosmos that lies outside our skins.[2]

During the seven decades since Bernard formulated this concept, there has been discovered feature after feature in our *milieu intérieur* to which his concept of physiological regulation must be applied. Vital phenomena involve the interplay of so many physical-chemical factors that only a beginning can be made towards enumerating them. The most important one is, of course, water itself, the chief constituent of the blood and tissues; then there are the numerous inorganic salts: sodium, potassium, magnesium, calcium, chloride, phosphate and bicarbonate, the delicate and precisely balanced acid and basic components, glucose and amino acids. This list, though incomplete, is long enough to emphasize the biological importance of the mixture as a whole. The lungs serve to maintain the composition of the blood with respect to oxygen and carbon dioxide, and with this their duty ends. The responsibility for maintaining the composition of the blood in respect to other constituents devolves

*This lecture is based in part on investigations cited in the bibliography, and in part upon unpublished studies of the fish kidney which are now being prepared for publication. A large part of the material upon which these studies are based was collected in 1930 while the author was a Fellow of the John Simon Guggenheim Memorial Foundation.

largely upon the kidneys. It is no exaggeration to say that the composition of the blood is determined not by what the mouth ingests but by what the kidneys keep; they are the master chemists of our internal environment, which, so to speak, they synthesize in reverse. When, among other duties, they excrete the ashes of our body fires, or remove from the blood the infinite variety of foreign substances which are constantly being absorbed from our indiscriminate gastro-intestinal tracts, these excretory operations are incidental to the major task of keeping our internal environment in an ideal, balanced state. Our glands, our muscles, our bones, our tendons, even our brains, are called upon to do only one kind of physiological work, while our kidneys are called upon to perform an innumerable variety of operations. Bones can break, muscles can atrophy, glands can loaf, even the brain can go to sleep, without immediately endangering our survival, but when the kidneys fail to manufacture the proper kind of blood neither bone, muscle, gland nor brain can carry on. To quote Bernard again, "In proportion as we ascend the scale of living beings, the organism grows more complex, the organic units become more delicate and require a more perfected internal environment". It was the view of this physiologist that we achieve a free and independent life, mentally and physically, because of the constancy of the composition of our blood. Recognizing that we have the kind of blood we have because we have the kind of kidneys that we have, we must acknowledge that our kidneys constitute the major foundation of our physiological freedom. Superficially, it might be said that the function of the kidneys is to make urine; but in a more considered view one can say that the kidneys make the stuff of philosophy itself.

Taken as a whole, the human kidney appears to be extra-

ordinarily complex, but on anatomical analysis this complexity is reducible to fairly simple terms. Each of the two kidneys, which are of about the same size, is made up of slightly more than one million microscopic units, or nephrons. (See Figure 1 of the preceding lecture.) These nephrons are all essentially alike and consist of a filtering bed composed of a capillary tuft, or glomerulus, which drains directly into a long, elaborate tubule. These million-odd glomerular-tubular units empty into common collecting ducts which through confluent union finally deliver the urine into the pelvis of the kidney, whence it flows down the ureter into the bladder. In the two million-odd glomeruli, i.e., in the renal filtering bed where the formation of urine begins, the blood is literally spread out over a great surface by being divided among the innumerable capillary channels. The total surface of the glomerular capillary bed in the two human kidneys exceeds 1.0 sq. meter. Through this bed there is filtered off in each minute's time about 125 cc. of water, or about 0.01 cc. per square centimeter per minute, which is a rate of filtration well below that of the ordinary laboratory filters. But this capillary bed is still a filter in the ordinary laboratory sense for it permits everything in the plasma to pass through it except the blood cells, the plasma proteins and similar large molecular aggregates. To supply this 125 cc. of filtrate 1300 cc. of blood are perfused each minute through the capillary bed of the glomeruli.

After leaving the glomerulus the blood passes into a second set of capillaries surrounding the tubule; here an opportunity is afforded for the tubule cells to transfer various substances from blood to tubular urine, or from tubular urine back into the blood, and here is where all specific chemical operations are carried out. For as the glomerular filtrate

passes down the tubules valuable substances such as glucose, sodium, chloride, amino acids, etc., are reabsorbed and returned to the blood by various processes of tubular reabsorption. At the same time certain waste products and foreign substances are taken from the blood by the tubule cells and transferred to the tubular urine. These excreted substances and such waste products and foreign compounds as are present in the original filtrate but are themselves not reabsorbed, remain in the tubular fluid to be excreted in the urine. Of all substances reabsorbed by the tubules water is reabsorbed to the greatest extent: out of the 125 cc. of filtrate formed each minute, on the average 124 cc. of water are reabsorbed, leaving only 1.0 cc. to be excreted as urine. In consequence of this extensive reabsorption of water, such substances as are filtered through the glomeruli but are themselves not reabsorbed by the tubules appear in the final urine in a highly concentrated form.[34]

In inquiring how the renal tubule elaborates the glomerular filtrate into urine it will be noted that this tubule is cytologically differentiated into three segments: a proximal segment, an intermediate thin segment, and a distal segment with drains into an arborized system of collecting tubules. The proximal segment appears to be a jack-of-all-trades, capable of reabsorbing valuable constituents, notably glucose and chloride, from the glomerular filtrate, and at the same time capable of transporting many waste products and foreign substances from blood to urine. On rather indirect evidence it has been inferred that the thin segment is responsible for the final reabsorption of water and the production of a highly concentrated urine. The function of the distal segment remains something of a mystery, but there are reasons to believe that it is responsible for the adjustment of the

acidity of the urine, for the conservation of the alkali reserve of the blood, and perhaps for the chemical synthesis of ammonia, hippuric acid, and other compounds which are manufactured locally by the renal tissue. In the present stage of our knowledge it would be dangerous to be dogmatic about details, and in any case it is not my intention to discuss the finer points of renal function. We are concerned here only with the general pattern of structure and function in this nephric unit, and with the inquiry, How did our kidney come to have the architecture that it does? In pursuit of this inquiry we must digress from the structure of the kidney to the general evolutionary history of the vertebrates, which history can appropriately be prefaced by a brief discussion of the structure of the earth.

According to the geologist the continents upon which we live are but irregular slabs of granite some 15 to 40 miles thick, floating like isolated islands upon a bed of basalt, the rock which makes up the oceanic floor. Under this bed of basalt, which is only some 700 miles thick, is a zone of semi-fluid magnum extending to a total depth of about 1800 miles. Innermost is a core of iron, some 4000 miles in diameter, which is raised far above incandescent heat (6,000°C.) by the enormous pressure existing at the center of the earth. It is now generally agreed by the geologist and the astronomer that the earth was separated from the sun about 2000 million years ago through disruption of the parent body by a passing star, but the daughter planet remained molten and homogeneous for only a short time, quickly acquiring its present stratified structure as it cooled and crystallized.

The continents float above the average level of the earth's crust because their granite is lighter than the basaltic bed upon which they rest; as their exposed masses weather down

and the silt is deposited in the sea along their edges, the added weight of this deposit causes the plastic basalt to flow beneath the land masses and to float them higher in the air. It is these slow adjustments to maintain isostatic equilibrium between the continents and the oceanic floor that sometimes cause abrupt movements of the land.[6,20] But all the earthquakes of historic time are trivial when compared with the disturbances of the past, which have extended not over days or weeks, but millions of years.

As measured, quite accurately it is now believed, by the radio-active clock within its rocks, the earth has had its present cold and semi-solid form for about 1800 million years. During this period it has been cooling and shrinking as a whole, having decreased in diameter something between 200 and 400 miles. Under the stresses resulting from this cooling process, and more particularly in consequence of the alternate fusion and solidification of the basaltic crust, this shrinking has been intermittent rather than uniform, so that at recurrent intervals of roughly 30 million years the continental masses have been wrinkled and folded into great mountain chains. During the intervening periods of geologic quiescence, the mountains raised by the preceding diastrophic movement have been largely if not entirely worn away to sea level by the slow erosion of wind and rain. Schuchert[29] estimates that the total continental depth eroded in this manner since the opening of the Paleozoic exceeds 75 vertical miles, or more than twenty ranges of mountains like the present European Alps or the American Rockies.

These periodic revolutions, as the geologist calls them, have made us what we are. Because they have changed the form and size of the continents and seas and at times submerged great areas of land beneath the water, because they have di-

verted oceanic currents, altered the dust and water vapor in the atmosphere, raised barriers to moisture-laden winds and otherwise interfered with the basal forces that control the weather, these revolutions have been accompanied by marked and protracted changes in climate over the entire surface of the earth. In general, periods of mountain building have been accompanied by marked refrigeration so that in some instances glaciers have descended to sea-level in equatorial latitudes; while in the quiescent intervals, after erosion had levelled the recently formed mountains to mere hills, warm shallow seas have transgressed widely over the low-lying lands, and even Arctica and Antarctica have enjoyed a climate that was warm and humid.[28]

According to modern experimental biology, the *vis a tergo* of evolution is the production of new varieties in consequence of random mutations in the chromosomes; such of these varieties as are unfitted to survive are pruned away by natural selection, leaving the better fitted mutants to get along as best they can. Mutation is fundamental to evolution, but mutation itself would be of little avail to modify organic pattern did not the *vis a fronte* of natural selection foster the survival of exotic individuals, of the new mutations, by offering them a special environment in which their unique characters are advantageous, by preserving them from genetic extinction through backbreeding with the unmutated forms, and probably in other ways. We may believe that in the shaping of the final evolutionary product as we find it, mutation and environment have played balanced and equal roles. Though we cannot assign to either mutation or selection any teleological direction, they tend within certain limits to have one result: after a few million years, when many millions of mutations have occurred and most of them have

become extinct, we can expect to find among the surviving organisms some that are much better fitted to endure severe environmental changes than was the parent form. It is only here, in the accidental development of increased independence of environment, of increased physiological freedom, in Bernard's sense of the word, that we can speak of evolution as being upwards, rather than just sideways.

The paleontological record reveals that evolution has not been a continuous process, but an intermittent one. In Lull's[21,22] descriptive terms, it has been a tide of organic specialization moving forward in marked pulsations invariably synchronous with the great upheavals of the earth's crust. It was probably one of these pulsations, synchronous with the Cambrian Revolution, that gave the vertebrates their start. The more important steps in the phylogenetic history of these forms, with special reference to those events that have a close bearing upon the evolution of the kidney, are depicted graphically in Figure 1.

The problem of the origin of the first chordates remains more or less where it was left by the great biologists of the past century—in a sadly unsatisfactory state. A few years ago there was consensus of opinion on at least one point: that the chordates shared with the echinoderms, the acorn worms, Branchiostoma (Amphioxus) and the tunicates, a common marine ancestor, a frail-bodied, ghostly form, similar perhaps to the Dipleurula lava of the echinoderms.[26] The most important features of this hypothetical ancestor were that it possessed a bilateral symmetry comparable to that of Branchiostoma, and like Branchiostoma it kept one end foremost as it swam slowly and feebly through the archaic seas. But the right of this ghostly form, the like of which no one has ever seen, to spawn the vertebrate phylum has been re-

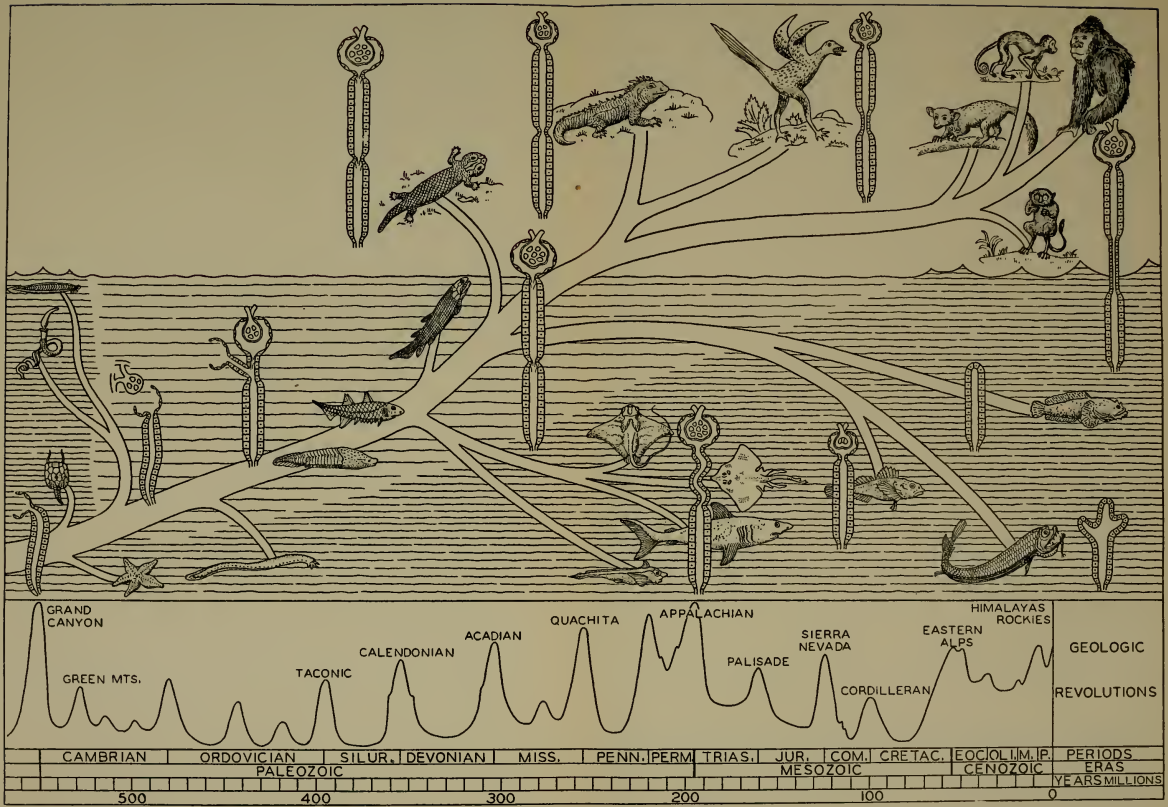
GRAND CANYON
GREEN MTS.
TACONIC
CALENDONIAN
ACADIAN
QUACHITA
APPALACHIAN
PALISADE
SIERRA NEVADA
CORDILLERAN
EASTERN ALPS
HIMALAYAS
ROCKIES
GEOLOGIC REVOLUTIONS
CAMBRIAN
ORDOVICIAN
SILUR.
DEVONIAN
MISS.
PENN.
PERM.
TRIAS.
JUR.
COM.
CRETAC.
EOCI
OL.
M.
P.
PERIODS
PALEOZOIC
MESOZOIC
CENOZOIC
ERAS
500
400
300
200
100
0
YEARS MILLIONS

FIGURE 1

cently questioned on the ground that the chordates, as they first appear in the fossil record, were depressed, bottom living, heavily armored and sluggish animals as far removed in appearance from Branchiostoma as one can imagine. This fact is in part responsible for the suggestion of Torsten Gislén[10] which has been seconded by Gregory[15,16] that the first chordates may have been evolved from a free-swimming paleozoic crinoid, or sea-lily. To this perennial debate we will add one more confusing argument of our own in a later paragraph.

As we cannot say from what forms the first chordates were evolved, neither can we with any certainty name the time of their evolution. Some would assign this evolution to the Ordovician Period, and some to the Cambrian. The opening of the Cambrian was marked by one of the most violent periods of mountain building the earth has ever known. These mountains have long since been washed away, but the sediment to which they were reduced is to be seen in the several vertical miles of red and yellow banded rocks through which the Colorado River has cut the Grand Canyon, and from which scenic chasm the geologic revolution takes its name. The biologist has repeatedly asserted that the truly unique features of the vertebrates consist, broadly speaking, of bilateral symmetry; of a stiffened and yet flexible internal backbone with an articulated skeleton for the support of muscles so arranged as to produce powerful lateral motions of the body, the backbone, skeleton and muscles being made up of regularly repeated segments; of paired, fin-like expansions of the skin to resist the thrust of these muscles and to maintain an even keel as the animal shoves itself forward in the water; and, of course, the major sense organs are located in the anterior end of the body. These features are just such

as to endow the organism with considerable swimming power, to enable it to move swiftly through the sea, or, as an alternative, to live in a swiftly flowing river. According to one theory, first propounded by Chamberlain[5] and substantially supported by Barrell,[1] the sluggish ancestors of the chordates had already migrated from the sea into the quiet brackish or fresh water lagoons of the Cambrian continents when the Grand Canyon revolution overtook them; the tilting of the land accelerated the motion of the rivers and this accelerated motion fostered the evolution of the dynamic, chordate form. But another theory, offered by Moody,[24] has it that the prochordates appeared in fresh water somewhat later, being literally driven into the rivers and lakes in Ordovician time by the attacks of the giant marine cephalopods that had then risen to supremacy in the seas.

Whichever theory we accept, it is now agreed that it was in the fresh waters of the Paleozoic continents, and not in the sea, that the first chordates, and from them the ostracoderms and early fishes, were evolved. When, in 1930, Professor E. K. Marshall and I reviewed the comparative anatomy of the kidney and on the question of the habitat of the early vertebrates followed the fresh-water thesis as set forth by Chamberlain and Barrel, we were conscious of treading on uncertain ground.[23] But since that time the subject has been carefully reviewed by Romer and Grove,[27] and in the face of this new evidence the fresh water hypothesis can no longer be denied.

Now, the very matrix of life is water, and the evolution of the kidney is essentially the story of the evolution of the regulation of the water content of the body. Marine invertebrates—worms, star-fish, molluscs, etc.—are generally in osmotic equilibrium with the sea, and they therefore face no

problem of water regulation. And it may safely be assumed that in the Cambrian or Ordovician prochordate ancestor of the vertebrates the kidney was little, if at all, concerned with the excretion of water, but wholly with the excretion of nitrogenous waste.

Judging from the evidence of comparative anatomy, the marine ancestor of the chordates had in each of the middle segments of the body a pair of open tubules which connected the primitive body cavity, or coelome, with the exterior; these segmental tubules were probably originally gonaducts serving to carry the eggs and sperm out of the coelomic cavity. Possibly before the chordate stage the coelomic membrane had come to play a part in excretion, and the segmental gonaducts which connected it with the exterior, and which were themselves formed by an exvagination of the coelomic membrane, perhaps participated in the regulation of the composition of the blood by reabsorbing valuable substances from the coelomic fluid, or by secreting waste products into this fluid as it passed out of the body.

With this rather meagre equipment of a coelomic membrane and a number of segmental ducts the first chordates essayed to enter the fresh waters of the paleozoic continents. In migrating from the sea to brackish estuary and thence up the rivers to the inland lakes these chordates were probably following a protoplasmic impulse to search for peace, but they were destined never to have that impulse satisfied. They encountered trouble, as is obviously revealed by the defensive armor which they soon evolved. The first vertebrates to appear in abundance in the fossil record, the Silurian and Devonian ostracoderms, the arthrodires, antiarchs and the earliest shark-like forms bearing jaws, the acanthodians, and even the later advanced fishes, were typically encased from snout

to tail in apparently impregnable armor which took the form of bony plates, scutes or scales. Any sample of the vertebrate population of Silurian-Devonian times from Pennsylvania to Spitzbergen suggests that some death-dealing enemy, swift, merciless and irresistible, lurked in every corner of the world.

Why all this heavy armor? As Romer[26] has pointed out, the only visible enemies of the ostracoderms and early fishes were the eurypterids that shared with them the continental waterways. Admittedly some of these eurypterids were much larger than the ostracoderms and fishes, and possessed strong claws, but they were primarily sluggish mud crawlers and unless they struck with their pointed tails, as does their enfeebled descendent, *Limulus*, or injected poison, as do their offspring, the scorpions, their fearsomeness may have been more apparent than real. The thesis that the armor of the early vertebrates served primarily to protect them from predacious enemies is perhaps open to question. May I offer an alternative suggestion: these vertebrates had an enemy which they could not see, but one which pursued them every minute of the day and night, and one from which there was no escape though they fled from Pennsylvania to Spitzbergen—a physical-chemical danger inherent in their new environment. When the first migrant from the sea took up residence in fresh water, its blood and tissues, bearing the physical-chemical imprint of its marine home, were rich in salts; for we may on straight extrapolation assume that at the opening of either Cambrian or Ordovician time the sea had one-half or better of its present salinity. This saline heritage might be in part erased, but it could not wholly be cast aside without re-organizing every nerve and muscle cell. The evolution of a regulated internal environment, if it had not yet begun, was imperatively imminent. For in the new fresh-water habitat

the salts and proteins of the tissue cells drew water by osmotic pressure so that by degrees the organism tended to pass from excessive hydration to edema and *in extremis* to swell to death. We may confidently assert that were the osmotic infiltration of water not arrested, survival in fresh water would be impossible. The first step towards arresting the infiltration of water would naturally be to insulate the body as far as possible by a waterproof covering. Why not believe that the ever-present armor of the fossilized vertebrates of Silurian and Devonian time was a defense against the osmotic invasion of fresh water rather than against the claws and tail-spines of the eurypterids?

In the history of evolution we see repeated instances where some adaptation is carried to absurd and disadvantageous overdevelopment, and perhaps an insulation serving primarily to repell fresh water may have been the genesis of spines and tubercles and other armored absurdities as would later serve to ward off strong-jawed, sharp-toothed predators such as had not yet been evolved. It seems that it was from certain of these protuberant spines that the fins were evolved. If we take this path of interpretation, we must conclude that what started out to be merely a waterproof insulation was destined to supply the fishes with fins for swimming, with an armament for battle, and the tetrapods with legs with which to crawl about on land.

But to invest the body in waterproof armor entailed important changes in internal anatomy as well. The multiple segmental openings of the archaic coelomic tubules had to be obliterated, and these tubules had to be arranged to drain into the one posterior member which still pierced the now armored skin. The evolution of the first archinephric duct may have been fostered by the waterproofing of the body.

Moreover, with most of the body covered by armor, a few posterior skeletal muscles had to be selected and developed in order to concentrate leverage in a powerful tail; this emphasis on the posterior segmental muscles, together with compression of the middle segments of the body cavity beneath one or a few armor sheets, would tend to obliterate the primitive segmental divisions of the coelome and foster the development of pericardial and splanchnic cavities as they occur in the higher vertebrates. The evolution of an armored body the remote, articulated parts of which had to be moved in a coordinated manner, would foster the evolution of a central nervous ganglion or brain, which stood in close functional relationship to the anterior, distance receptors. The development of armor about the head would foster the cranial articulation of mouth parts and the evolution of jaws, which, absent in the ostracoderms, are first discoverable in the mailed acanthodians of Silurian time. But these interesting speculations, and they are nothing else, lie apart from our main theme, that it was in seeking protection against fresh water that the first vertebrates to be preserved in the fossil record, the ostracodermns, came to be depressed, bottom-living armored creatures far removed from the hypothetical dynamic, fast-swimming prototype of classical theory. For even under their best efforts at free swimming the early armored vertebrates found it easier to sink to the bottom and wiggle upon the mud, where indeed most of them remained until the close of the Devonian. If the ostracoderms are viewed as a consequence rather than a beginning of vertebrate evolution they offer less difficulty to the dynamic theory, which is recommended on so many grounds.

Yet even thus encased in a waterproof covering, the gills, the mouth and the intestinal tract still afforded routes by

which excessive quantities of water could be absorbed, and the ostracoderms and early fishes had to compensate for this excessive influx by increasing the excretion of this substance. Their battle against fresh water was only half won. Evolution frequently works by adapting old things to new uses, and it seems that no better way could be devised to get the surplus of water out of the body than to have the heart pump it out; and the easiest way to do this was to prepare a filtering device by bringing the pre-existing arteries into close juxtaposition with the pre-existing coelomic tubules, to form the coelomate glomerulus which, as a lobulated tuft of capillaries, still hangs free in the pericardial cavity of some of the lower vertebrates. Later a direct connection was effected between arteries and tubules outside the coelomic cavity, to form the typical glomerulus as found in mesonephros and metanephros of the higher animals. But in many recent fishes and Amphibia, the mesonephric tubules still retain their ancient connection with the body cavity. The essential point is that the renal glomerulus was evolved independently of, and long after the evolution of the renal tubule. And it will be recalled that in the ontogenetic development of the human embryo the glomerulus is not brought into conjunction and connected with the tubule of the metanephros until some time after this tubule has been formed; it is possible that this interval between the development of the tubule and the glomerulus is an ontogenetic recapitulation of the phylogenetic interval which separated their evolution some four or five hundred million years ago.

But the very nature of a high-pressure filtration system permits not only water to be pumped out of the body, but also most of the osmotically active constituents of the plasma, which means all the valuable constituents except the proteins

—glucose, chloride, phosphate, etc.,—for if these did not pass through the filtering bed the great osmotic pressure which they exert would effectively prevent the heart from pumping any water through this bed. Hence, with the advent of the glomerulus it was necessary so to modify the tubules that they could reabsorb these valuable constituents from the filtrate. Moreover, there was such an excess of water over salt to be excreted that the urine had to be almost pure water, i.e., it had to have a substantially lower osmotic pressure than the blood. Thus, as a concomitant of the evolution of the glomerulus, there came into existence a tubule capable of reabsorbing large quantities of glucose and similar valuable substances, and capable of elaborating, by the reabsorption of salt, a urine that was hypotonic to the blood.

To whatever extent this new fresh water kidney was adequate to its time, times changed. The restless earth began to heave again. At the close of the Silurian another diastrophic movement disturbed its crust; no great mountains were raised in North America, but a ridge higher than the Alps was wrinkled up in Northern Europe, of which the low Caledonian mountains of Scotland are all that now remain. Other continental areas were extensively submerged beneath the sea, and what land escaped was plagued by extremes of climate swinging between excess of rain and drought. The fishes of the early and middle Devonian found themselves forced to choose between the invading salt water marshes and the isolated fresh-water pools which periodically contracted into stagnant swamps or hard mud flats. Some of the more powerful elasmobranchs, perhaps now better fitted to compete with the cephalopods and other marine invertebrates, sought sanctuary by turning towards the sea; the fate of these, the first fishes to live in salt water, will be noted in a

later paragraph. The more advanced of the fishes, however, in order to survive in the stagnant waters of the continents, took to swallowing air and thus invented lungs and prepared the way for the evolution of the terrestrial vertebrates.

At the close of the Devonian the earth suffered its third major upheaval in vertebrate history; the periodic dry spells of the Devonian were replaced by protracted and widespread dessication and many of the air-breathing fishes followed the example of the Silurian elasmobranchs and abandoned fresh water for refuge in the sea where they founded the Paleozoic-Mesozoic dynasties of marine teleosts. But certain of the fresh water fishes, the Crossopterygians, learned to use their fins for feet with which to crawl from one pool to another, and thus founded the Carboniferous and Pennsylvanian Amphibia which needed to return to the water pools only occasionally to drink and to lay their eggs.

For a moment let us consider what must have happened to the bony fishes that took up life in the sea in the Carboniferous. Actually, none of those Mesozoic forms survives today, all the recent marine teleosts having been evolved since the opening of the Cenozoic era, but the physiology of these recent forms is adequate to illustrate the difficulties of changing one's habitat from fresh to salt water.

With the migration from fresh to salt water the osmotic relations between organism and environment are reversed; the body tissues are less concentrated than the sea, and unless the composition of these tissues is completely overhauled, they must tend constantly to suffer osmotic dehydration and ultimate dessication and collapse. The marine bony fishes face not a perpetual excess of water, like their fresh water ancestors, but a perpetual deficit of it. In theory they could maintain the accustomed proportion of salt and water in the

body by excreting a highly concentrated urine, but in practice they cannot do this for the fish kidney is unable to elaborate a urine which is osmotically more concentrated than the blood. Their lot would be as unhappy as that of the Ancient Mariner were it not that, unlike that thirsty man, they have the happy advantage of possessing gills, and the gill is the only organ in the lower vertebrates capable of doing hypertonic osmotic work. Had the Ancient Mariner possessed such a marvelous organ he could have lived like a fish by drinking the briny sea; he could have separated the salt from the water by excreting the salt out of his gills in a concentrated form, leaving the water free for his tissues, or for the formation of urine. But with the limitations of the fish kidney he still would have had cause to deplore his lot, since for every liter of urine formed he would be forced to concentrate a liter of sea water by 66 per cent. It is not surprising that the marine fishes, rather than spend their precious energy in making more concentrated sea water out of the already concentrated sea, naturally became conservative in the matter of urine formation and excreted no more urine than was required to remove waste products from the body.[31] When the bony fishes migrated from fresh water to the sea, the high-pressure filtering device of the glomerulus was no longer an asset, but a liability. They shut the filtering bed down as far as possible, and with the passing years the glomeruli grew smaller and smaller, fewer and fewer; to examine the glomeruli in a series of marine teleost kidneys reminds one of the old-fashioned Herpecide advertisement: Going — going — gone! Nearly all the marine teleosts show some evidence of glomerular degeneration, and in certain of them (the toadfish, midshipman, goosefish, batfish, sea horse, pipefish, and in certain deep sea fishes) the kidney has become entirely aglo-

merular.[8,12,13,14,23] There is no constant rule by which the aglomerular condition is reached; Grafflin[11] has shown that in the "daddy" sculpin the glomeruli cease to function between the young and the adult stage, while Armstrong (personal communication) has shown that in the toadfish and pipefish a glomerulus does not develop even in the embryo. Though evolution is not reversible, the marine teleosts are indirectly converting their kidneys back to the purely tubular form possessed by the prochordate ancestor which left the sea in Cambrian or Ordovician time.

But there is more than one way of solving physiological difficulties, including that faced by the Ancient Mariner and the marine teleosts. Let us return to the elasmobranchs, who had first made the marine migration in the Devonian. These more primitive fishes solved the problem of living in salt water in an entirely different way. The four orders of the sub-class Elasmobranchii—the sharks' rays, skates and chimaeras—separated from the parent stem and from each other in or shortly after the Devonian period; that is to say, the Devonian is the most recent time at which we can assign to all four orders a common ancestry. Yet all four orders possess a common and surprisingly unique adaptation for living in seawater; they have changed the composition of their blood by deliberately bringing themselves, as it were, into a perpetually uremic state; they reabsorb from the glomerular filtrate as it passes down the tubules such urea as is present in this fluid (urea being the chief product of nitrogen combustion) much as the Ordovician-Silurian fishes learned to reabsorb glucose and chloride. They return this otherwise inert waste product to the blood until it reaches concentrations of 2000 to 2500 mgm. per cent. The presence of this urea raises the osmotic pressure of the blood above that of the

surrounding sea water and causes water to move from the sea into the body, through the gills; and thus, pure water, free from salt, moves continuously inward at a sufficient rate to afford a vehicle for the urinary excretion of waste products and such excess salt as is present in the food.[32,33] Where the bony fishes must continuously drink sea water in a steady stream, in the elasmobranchs this fluid serves only to wet the gills.

A unique tubular segment is present in the elasmobranch kidney, just distal to the glomerulus, which is thought to be the site of the active reabsorption of urea from the glomerular filtrate. None of the elasmobranch fishes, in spite of their long residence in the sea, is aglomerular; having always had abundant water available for filtration, there has been no need to abandon their glomeruli.

It is especially interesting that the method of reproduction in this subclass is highly specialized, the majority of the Elasmobranchii being viviparous, the rest producing an egg inclosed in a relatively impermeable egg case. The latter is apparently the more primitive mode of reproduction. Both the viviparous forms and those that have a cleidoic or "closed" egg utilize internal fertilization, for which purpose there exist claspers in the male and accessory reproductive glands in the female. One supposes that this specialized mode of reproduction is concerned with the conservation of urea in the young embryo until such time as its kidneys and its respiratory and integumentary membranes are organized. The Cladoselachii of the Devonian apparently lacked claspers, but these were present in the Carboniferous and Permian hybodonts and pleuracanths and in all the Jurassic sharks. Further paleontological research may, in the above view, be able

to reveal to us the exact time at which the uremic habitus, as an adaptation to salt water, was acquired.

Returning now from the fishes to the main evolutionary tree: during the coal-ages the low-lying lands were heavily clothed in tropical and subtropical vegetation. There was a high rainfall, the air was humid, the world was a swampy paradise inhabited by spiders, scorpions, centipedes and snails, and lorded over by Amphibia that lived half in water and half on land. But on the whole life was as stagnant as the swamps in which it lived. It was too comfortable, and in comfort the living organism comes to rest, its evolution stops or regression begins.

The moist paradise of the coal ages lasted until the Permian; then in the great Appalachian Revolution a majestic range of mountains, 3 to 4 miles high, was corrugated in the region that now lies between Newfoundland and Alabama. The Southern Hemisphere passed into a severe glacial period, and in the Northern Hemisphere the warm moist climate of the Carboniferous was replaced by aridity and seasonal chilliness. The cycads, equisetums, clubmosses and tree ferns of the coal measures were exterminated; all the great families of the marine elasmobranchs were destroyed along with most of the marine and fresh water teleosts; and the stagnant Amphibia changed slowly towards more terrestrial forms. It was the sheer pressure of world-wide Permian dessication that fostered the evolution of the reptiles which were driven *in extremis* to living permanently on land. These new reptiles had tough hides and relatively long legs with which to crawl from one water hole to another; the egg, for the first time in vertebrate history, was encased in a waterproof shell and contained within it the allantoic sac to receive the waste products

of the embryo; a multitude of adaptations, most of which concern the preservation of the internal environment, had to be effected to liberate the organism from its original aquatic heritage. One of the most important of these adaptations consisted in a subtle change in the method of protein combustion. Instead of degrading protein nitrogen to urea, as had the fishes and Amphibia, the reptiles overhauled their metabolic machinery and degraded their protein nitrogen to uric acid. Uric acid is a very peculiar substance: it is almost insoluble in water, and yet it readily forms highly supersaturated solutions; the reptiles secrete it in the tubular urine as a concentrated, supersaturated solution, then as the tubular urine passes to the cloaca the uric acid precipitates out, leaving most of the water in the urine free to be reabsorbed into the blood, while the uric acid itself is expelled as an almost dry paste. This same uric acid adaptation, like so many other reptilian characters, is found in the birds,[19,35] for the birds are but warm blooded reptiles with feathers and wings.

When the teleosts faced dessication in the briny sea many of them completely discarded their luxus glomeruli. In view of the fact that in the arid-living reptiles and the marine birds the need for water conservation is equally extreme one might expect some of them to be aglomerular too, but no aglomerular reptile or bird has thus far been described. The reptilian-avian kidney is, however, headed in that direction, for the once elaborate glomerular tuft is reduced to a few, in some cases only two, capillary loops, and contains a great amount of inert connective tissue. It is as though these animals, having found the glomeruli largely superfluous but needing to flush the uric acid-rich secretion of the tubules down to the cloaca, had stopped short of the complete obliteration of the glomeruli and retained a vestige of the filtering

bed in order to supply the tubules with a feeble, irrigating stream.

At this point you are probably wondering if the title of this discourse is not misrepresenting, since so much of it has been devoted to the lower vertebrates and so little of it to the mammals or to man. I would defend this apparent unfairness by pointing out that all the mammals together constitute but a small fraction of the vertebrates, and man himself but a single mammalian species. The geological age of truly human forms is at most 1,000,000 years, a slight interval indeed out of the 500 to 600 million years which we must apprehend if we are to see the human organism in the proper perspective. But apart from this aspect of the problem I must confess that at this point in the story of the evolution of the kidney there is a serious hiatus in our knowledge, namely, the circumstances surrounding the evolution of the first mammalian forms.

The mammals have added the only important patent to the kidney since Devonian time: the capacity to excrete urine that is markedly hypertonic, or osmotically more concentrated than the blood. As pointed out in an earlier paragraph, the elaboration of this hypertonic urine is probably effected by the unique, intermediate thin segment which is present in the tubule of all mammalian forms.

We must inquire, how did this capacity to excrete a hypertonic urine come to be evolved? And we may go on to ask, since the mammals were evolved from reptilian forms, why do they not excrete uric acid like the reptiles and the birds? And since the mammals do not generally live in fresh water, since in fact some mammals, such as the kangaroo rat, can live indefinitely upon dry oatmeal, while others, such as the whales and seals, can live indefinitely in the sea without

ever taking a drink of fresh water, why have they not lost their glomeruli? Why, on the contrary, have the glomeruli reached their fullest development in the order Mammalia?

Let us review briefly what is known about early mammalian evolution. Through all the Mesozoic the mammals remained in the background and let the reptiles have the stage. During the dessication of the Permian these thick-skinned animals, their legs ever growing longer, began to crawl on their bellies all over the world, and to establish their reputation for grotesquerie. In the Triassic, which was, like the Permian, a period of aridity but one lacking marked seasonal extremes of heat and cold and generally warm enough to permit the luxuriant growth of ferns, tree ferns and equisetums, reptilian peculiarities began to reach extremes. The more advanced took to walking on their hind legs and strutted about like the lords of the universe. In the Jurassic the climate reverted to subtropical humidity, and the reptilian paradise was but slightly disturbed by the diastrophic movement that raised the Sierra Nevadas and ushered in the Cretaceous. Here reptilian evolution culminated, on the one hand, in the great dinosaurs, the most magnificent creatures and probably the dumbest per kilogram of body weight that the earth has ever seen, and, on the other hand, in the flying reptiles whose jaws were still filled with teeth and whose front feet were still tipped with claws. Then, at the end of the Cretaceous, when the Rocky Mountains and the Andes were slowly rising, the curtain is rung down on this Mesozoic scene with a suddenness that is almost dramatic. The dinosaurs dissappeared, the birds lost their teeth and shaped their forelimbs into delicate wings, and a host of new actors, in the form of the Cenozoic mammals, rushed

upon the stage as though they had long been waiting impatiently behind the scenes.

Where these mammals had been throughout the long and fantastic period of the Mesozoic is still a mystery. The oldest known mammalian fossils date from the late Triassic or early Jurassic periods, and these were already advanced and specialized creatures; no remnants of a stock which could have been ancestral even to the Cretaceous forms have been discovered.[30] However, it must be believed that truly mammalian types were in existence in the early Triassic, and probably even in the Permian, while the reptiles themselves were still in a relatively primitive stage. Certain Triassic reptiles, the cynodonts, resembled the mammals in such features as the posterior jaw elements, the teeth, and the structure of the shoulder girdle, and they stood with their limbs well under the body, and it may be supposed that the cynodont reptiles and the mammals were evolved out of a common Permian stock. It need not be supposed, however, that this common ancestral stock was warm-blooded, but neither must it be supposed that it had acquired the reptilian habit of excreting uric acid; rather it may have been a semi-aquatic type that degraded its protein nitrogen to urea, as we may suppose was the case in the Pennsylvanian Amphibia.

Proceeding from this premise, it is to be noted that there were two environmental stresses operating in Permian time: intense aridity and intense frigidity. The Permian was one of the greatest ice ages of all time. Frigidity—the cold nights of the desert and the long, cold, seasonal winters—placed a high premium upon the ability to be continuously active, even as aridity placed a premium upon the ability to travel overland from one water hole to another. A nascent, evolving stock might possibly have adapted itself to one of these

stresses ahead of the other. Let us suppose that the proto-mammalian forms got off to warm-bloodedness first, in adaptation to frigidity, rather than to uric acid excretion, in adaptation to aridity. The progressive evolution of warm-bloodedness entailed a marked increase in the circulation of the blood, which in turn entailed a corresponding increase in arterial blood pressure; this increased blood pressure resulted in an increased rate of filtration through the glomeruli, and this entailed an increased need for conserving water by reabsorbing it from the tubules. Rapid elevation of body temperature, it would seem, would foster increased reabsorption in the tubules by accentuating the very need for it. It is plausible, therefore, that the thin, intermediate segment of the mammalian tubule with its accentuated capacity for reabsorbing water was simply a sequel of the evolution of the warm-blooded state, which evolutionary step may have been taken before the habitus of uric acid excretion had become fixed in the general reptilian stock. Once the intermediate segment of the mammalian kidney had been evolved as an adaptation to frigidity, it served as an adaptation to aridity as well, for the enhancement of water conservation which it effected enabled the mammals to compete, dry spell for dry spell, with the more sluggish reptilian forms. Into whatever dry spot the reptiles could radiate, the mammals could follow them, and when the desert night descended and forced the cold-blooded reptiles into sleep, the warm-blooded mammals remained active and alert. But more important, perhaps, was the change in temperature that marked the Laramide revolution; it may have been the inability of the reptiles to endure this period of refrigeration and dessication that led to their almost total extinction,[25] while the furry warm-blooded mammals, equipped to meet both vicissitudes, could carry on.

This interpretation receives support in the fact that in the bird kidney the tubules are of a mixed type, some resembling the reptilian tubule in lacking a thin segment, some resembling the mammalian tubule in possessing such a segment. Functionally the bird kidney is intermediate between the reptiles and the mammals, the bird retaining the uric acid habitus of the former, although it can under certain conditions elaborate a distinctly hypertonic urine.[19] The similarity to the mammalian kidney in the last respect is probably a case of convergent evolution fostered by the common character of warm-bloodedness, for the birds were evolved from reptiles that were far removed from the mammalian stem.

When, at the close of the Cretaceous, the dinosaurs became extinct, the mammals began to populate the earth. In the Paleocene the lemuroids took to living in the trees and became the Eocene tarsioids who looked forward with both eyes at the same time and depended upon the sense of sight rather than upon smell or hearing. In the Oligocene a tarsioid or lemuroid stock gave rise to the monkeys which in the Miocene in turn spawned the Dryopithecine apes that roamed over Europe, Africa, and Asia. Then the rising Himalayas buckled central Asia into an uninhabitable mountain chain, and such of the Dryopithecine apes as survived were driven to abandon the trees and to seek their living in the southern plains. From Asia a Dryopithecine descendent migrated into Africa, to spawn there in the Pliocene such forms as *Australopithecus africanus,* discovered by Dart,[7] and *Plesianthropus transvaalensis* and *Paranthropus robustus,* discovered by Broom[3,4] in 1938, and declared by their discoverers and by Gregory and Hellman[17] to be truly neither ape nor man. (For a general discussion of the origin of man see 36.)

The kidney is not identical in structure and function in

all mammalian forms, but the human kidney differs only in details from that organ in the dog, cat, and rabbit. It is not surprising that in function the human kidney has its closest homologue in the kidneys of the great apes, who can claim with man a common ancestor back somewhere in the Miocene.

Examining the pattern of the human kidney, we must not be surprised to find that it is far from a perfect organ. In fact, it is in many respects grossly inefficient. It begins its task by pouring 125 cc. of water into the tubules each minute, demanding for this extravagant filtration one third of all the blood put out by the heart. Out of this veritable Niagara of water, 99 per cent must be reabsorbed again. This circuitous method of operation is peculiar, to say the least. At one end, the heart is working hard to pump a large quantity of water out of the body; at the other end the tubules are working equally hard to defeat the heart by keeping 99 per cent of this water from escaping. Thus heart and kidney are literally pitched in constant battle against each other—our lives depend on neither one of them ever winning out. Nature frequently opposes two forces against each other in order to maintain a steady state, but the opposition in this instance takes on an aspect of sheer extravagance. Paradoxically, the kidney has to do its greatest work when it excretes the smallest quantity of urine; as the urine flow increases it does less and less work, and if the urine flow were to increase to the collossal figure of 125 cc. per minute—170 liters per day—the kidney, in respect to the excretion of water, would be doing no work at all.

In consequence of the circuitous pattern of the filtration and reabsorption of water, nearly half-a-pound of glucose

and over three pounds of sodium chloride per day, not to mention quantities of phosphate, amino acids and other substances must be saved from being lost in the urine by being reabsorbed from the tubular stream. There is enough waste motion here to bankrupt any economic system—other than a natural one, for Nature is the only artificer who does not need to count the cost by which she achieves her ends.

The chief waste product which the kidney is called upon to excrete is urea. The glomeruli remove each minute such urea as is contained in 125 cc. of blood, but because of the way the tubules are put together fifty per cent of this urea diffuses back into the blood again, so that in terms of the total renal blood flow (1300 cc. per minute) the over-all efficiency of the excretion is only about 5 per cent. There are certain foreign substances, however (diodrast, hippuran, phenol red, etc.), which have been synthetized only within the past few years, which the kidney excretes with almost 100 per cent efficiency. Is it not strange that, in spite of the fact that it has never before encountered them, the kidney should be able to excrete such artificial synthetic compounds twenty times as efficiently as it excretes the principle nitrogenous waste product naturally formed in the body, and which it has been excreting for millions and millions of years?

The kidney is receiving more attention today than ever before. These scientific problems range from local organic pathology to such subtle matters as the relation of the internal environment and its multiplicity of chemical factors to personality and mental disease. Certainly, mental integrity is a *sine qua non* of the free and independent life. As intermittent rays of light blend into moving images on the cinematographic screen, so the multiform activities within the

brain are integrated into images of consciousness and brought into an unstable focus to form that fleeting entity which we call personality, or Self. But let the composition of our internal environment suffer the slightest change, let our kidneys fail for even a short time to fulfill their task, and our mental integrity, our personality, is destroyed.

There are those who say that the human kidney was created to keep the blood pure, or more precisely, to keep our internal environment in an ideal balanced state. I would deny this. I grant that the human kidney is a marvelous organ, but I cannot grant that it was purposefully designed to excrete urine, nor even to regulate the composition of the blood, nor to subserve the physiological welfare of *Homo sapiens* in any sense. Rather I contend that the human kidney manufactures the kind of urine that it does, and it maintains the blood in the composition which that fluid has, because this kidney has a certain functional architecture: and it owes that architecture not to design or foresight or any plan, but to the fact that the earth is an unstable sphere with a fragile crust, to the geologic revolutions that for 600 million years have raised and lowered continents and seas, to the predacious enemies, and heat and cold, and storms and droughts, the unending succession of vicissitudes that have driven the mutant vertebrates from sea into fresh water, into dessicated swamps, out upon the dry land, from one habitation to another, perpetually in search of the free and independent life, perpetually failing for one reason or another to find it.

It is more than an antiquarian impulse that leads me to close this lecture by two quotations. About the 5th century, a Persian philosopher who is well known to all of you remarked:

"Myself when young did eagerly frequent
Doctor and Saint, and heard great argument
about it and about: but evermore
Came out by the same door where in I went."

Many centuries later, specifically in 1804, a French chemist named Fourcroy,[9] who presented the first comprehensive exposition of the nature and physiological importance of urine in a volume entitled, "A General System of Chemical Knowledge", said:

"The urine of man is one of the animal matters that have been the most examined by chemists and of which the examination has at the same time furnished the most singular discoveries to chemistry, and the most useful applications to physiology, as well as the art of healing. This liquid, which commonly inspires men only with contempt and disgust, which is generally ranked amongst vile and repulsive matters, has become, in the hands of the chemists, a source of important discoveries and is an object in the history of which we find the most singular disparity between the ideas which are generally formed of it in the world, and the valuable notion which the study of it affords to the physiologist, the physician and the philosopher."

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STUDIES IN THE PHYSIOLOGY OF THE KIDNEY

THE RENAL BLOOD FLOW IN NORMAL AND HYPERTENSIVE SUBJECTS

THE RENAL BLOOD FLOW IN NORMAL AND HYPERTENSIVE SUBJECTS

It is appropriate to apply the methods which have been described in the previous lecture in a few experiments that throw light upon the physiological control of the renal blood flow.

The first experiment which I would like to discuss concerns the effects of oil of juniper on renal function (Figure 1). Many years ago oil of juniper enjoyed a vogue as a diuretic, which fact led us to suspect that it might have some action on the renal circulation. (The experiment serves chiefly to illustrate the method of examination.) The subject was prepared for the determination of renal clearances in the usual manner. He was well hydrated by the copious administration of water, both the night before and early in the morning of the examination, in order to establish good urine flows. Suitable plasma concentrations of diodrast and inulin were maintained by continuous intravenous infusion, and urine was collected by catheter, the bladder being rinsed out with saline at the end of each urine collection period. The data recorded in the figure are the cc. of plasma cleared per minute of diodrast (D) and inulin (IN), the filtration fraction (FF), the brachial blood pressure, and, at the bottom the urine flow in cc. per minute (V). The diodrast clearance indicates the renal plasma flow, the inulin clearance the rate of glomerular filtration, the filtration fraction the per cent of plasma filtered through the glomeruli.

As shown by the three control periods at the left of the chart, he had a basal renal plasma flow averaging 782 cc. per minute. The administration of 1 cc. oil of juniper had no effect on either the renal plasma flow or the filtration rate.

The urine flow (V) increased transiently from slightly above 1 cc. to above 8 cc. per minute; whether this diuresis is attributable to local action of the oil of juniper upon the renal tubules, or to a reduction in the secretion of the antidiuretic hormone of the posterior pituitary gland in consequence of reflex excitation from the gastro-intestinal tract, is undetermined, though the latter seems the more likely explanation. The phenomenon of diuresis is, however, of secondary importance; changes in urine flow represent merely slight changes in the reabsorption of water from the glomerular filtrate, and since such changes can be elicited by many different types of stimuli acting through the supraoptic-hypophyseal mechanism, they have little fundamental significance with regard to renal function. What we were looking for

FIGURE 1

FIGURE 1. Action of oil of juniper on effective renal plasma flow, (D=diodrast clearance in cc. per minute), filtration rate (IN=inulin clearance in cc. per minute), filtration fraction (FF=inulin/diodrast clearance ratio), blood pressure (BP in mm. Hg) and urine flow (V in cc. per minute). (From 6).

when we did this experiment was a change in renal plasma flow, but in this respect the experiment was entirely negative. The slight parallel variations in the diodrast and inulin clearances are probably not real fluctuations in activity but errors due to incomplete emptying of the bladder.

We have in our records a considerable number of such negative experiments, for we have had occasion to examine the action of a number of drugs upon renal function in our search for certain desired effects, and usually this has been the result. But these negative experiments at least enable us to say that the renal plasma flow and filtration rate in a normal individual can be expected to remain quite constant over a two or three hour interval, or for that matter, in repeated examination at widely separated intervals. One subject examined in the basal condition on 12 occasions over a period of 4 months has shown an extreme variation of only ± 15 per cent from the average figure. Assuming a constant basal or resting blood pressure, this fact merely bespeaks the stability of the vascular bed of the kidneys.

We may go farther than emphasizing the constancy of the renal blood flow in any one individual: it is in fact quite uniform in different individuals. In comparing 34 normal subjects which we have examined in the basal condition up to the present time, the standard deviation, counting each individual but once, is 16 per cent of the mean. The mean value is 737 cc. of plasma, or 1275 cc. of whole blood per minute, which is about one-third of the basal cardiac output. Though this uniformity in renal blood flow is not wholly unexpected on an anatomical and physiological basis, the absolute magnitude of 1275 cc. has been rather surprising. It is, however, no greater than might be expected from observations on anesthetized animals.

Were I to tax your patience by showing a fair sample of our negative experiments, such as the one given in Figure 1, you would be prepared to believe, as indeed we at times have been tempted to believe, that the renal circulation and the glomerular apparatus are so constructed as to be incapable of variation. So I pass immediately to the demonstration that

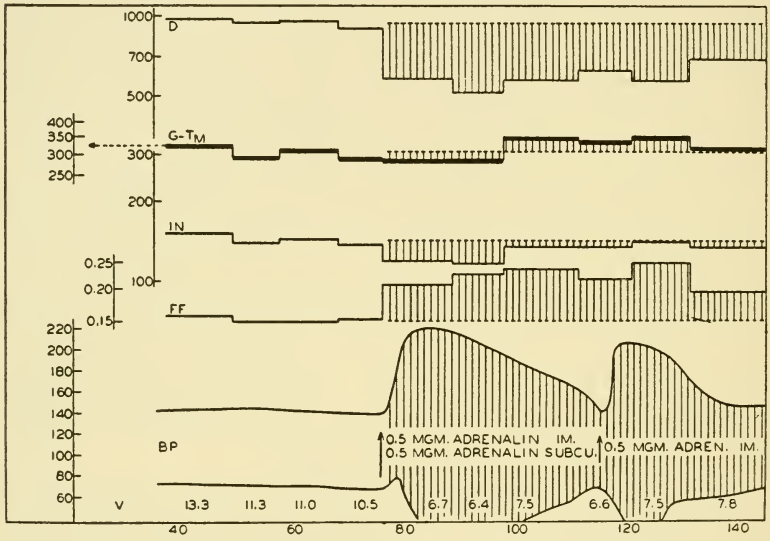

FIGURE 2

FIGURE 2. Action of adrenin on effective renal plasma flow, etc. Legend as in Figure 1. G-Tm=maximal rate of tubular reabsorption of glucose under conditions of tubular saturation, in mgm. per minute. G-Tm is measure of the number of active glomeruli in the kidney.

the renal circulation can be profoundly altered, and I have selected for this demonstration the action of that dynamic hormone, adrenin (Figure 2). The subject of this experiment showed in four control periods an average renal plasma flow of 926 cc. per minute. Adrenin (0.5 mgm, intramuscularly and 0.5 mgm. subcutaneously) reduced the plasma flow to a minimum of 510 cc. (i.e., to 55 per cent of the control

value), and in view of the fact that the mean brachial blood pressure was not lowered, it must be concluded that this reduction in renal plasma flow was due to constriction of the arterioles of the kidney, either on the afferent or efferent side of the glomeruli. The locus of the constriction can, we believe, be identified from the available data. Had the afferent arterioles been constricted the glomerular pressure would have been reduced, and consequently the filtration fraction would have fallen, while efferent constriction would have raised the glomerular pressure and increased the filtration fraction. The fact that the filtration fraction rose rather than fell is therefore evidence that it was the efferent rather than the afferent arterioles which were constricted. Since the filtration fraction increased almost in the same proportion as the plasma flow was reduced, the filtration rate remained almost unchanged, and had we observed the filtration rate alone we might have concluded that adrenin has no effect upon the kidney. Here we have a demonstration of an important fact about the glomerular circulation. The construction of the glomeruli is such that when the renal blood flow is altered in consequence of changes in efferent arteriolar tone, the simultaneous and opposite changes in glomerular pressure tend to maintain the filtration rate at a constant level. The filtration rate in normal man is remarkably constant, even more constant than the renal blood flow; and this constancy may be attributed to the circumstance that changes in renal blood flow appear to be mediated by changes in the tone of the efferent, rather than the afferent, glomerular arterioles.[6] This unique feature of the glomerular apparatus is of considerable importance since extreme changes in renal blood flow may occur in the diseased kidney with practically no change in the filtration rate.

In passing, may I comment on the effect of adrenin upon the blood pressure. It is still frequently stated that adrenin raises the systolic pressure because it is a vasoconstrictor drug. Admittedly it constricts the efferent arterioles of the kidneys, as shown here, as well as the arterioles of the skin; it probably also constricts the spleen and some of the venous reservoirs. But it dilates the arterioles in the skeletal muscles and possibly in some of the viscera, and because of the larger fraction of the vascular bed involved in these regions the net effect of this dilatation is quantitatively preponderant over such vasoconstriction as may occur. Consequently the mean peripheral resistance is substantially *reduced,* as has been adequately demonstrated by several groups of investigators.[19,30,32] So far as the net effect of relatively large doses in man is concerned, adrenin must be considered as a vasodilator drug, this vasodilatation being evidenced typically by a fall in the diastolic pressure. In this particular experiment the diastolic pressure fell to undeterminable levels. The rise in systolic pressure must be attributed to increased cardiac output in consequence of increased heart rate and increased stroke volume, the increased stroke volume in part being attributable to increased venous pressure. If the cardiac output is sufficiently increased the diastolic pressure may be maintained at its control level or even momentarily increased.

There is included in this experiment a series of measurements of glucose-Tm (G-Tm) obtained by maintaining the plasma glucose at 380-445 mgm. per cent. During the four control periods this value averaged 306 mgm. per minute; during the action of adrenin it averaged 325 mgm. per minute, i.e., it increased by 6 per cent, an increase of doubtful significance. Glucose-Tm, you will recall, is a measure of the number of active nephrons which are reabsorbing glucose.

Had adrenin closed any glomeruli by its vasoconstrictor action, this figure would necessarily have been reduced, regardless of any changes in the filtration rate in the remaining active nephrons. The failure of glucose-Tm to decrease shows that adrenin in this dose (which is about the maximal dose which may be administered to man without serious disturbance) did not close any glomeruli.

We have examined a number of so-called sympaticomimetic drugs, but the only other one of immediate interest is

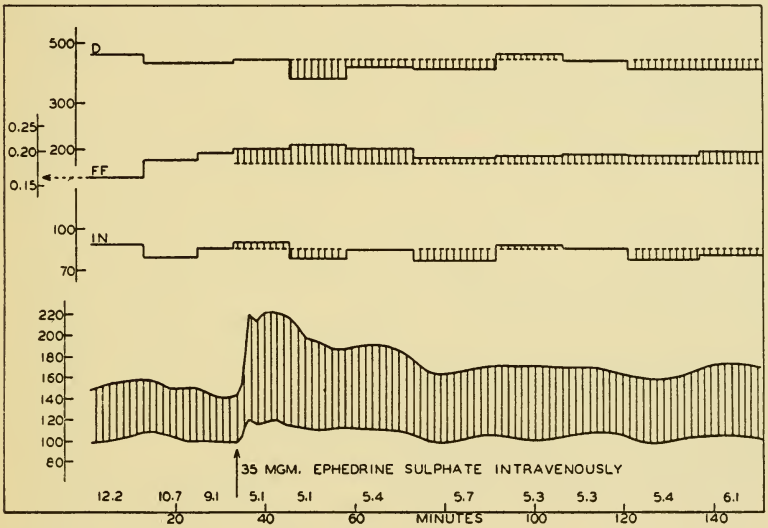

FIGURE 3

FIGURE 3. Action of ephedrine on effective renal plasma flow, etc. Legend as in Figure 1.

ephedrine (Figure 3). The net effect of this drug in man is, like that of adrenin, vasodilatation, as evidenced by a decrease in the total peripheral resistance.[30] We have been rather surprised to find that ephedrine in therapeutic doses has no or negligible effect upon the renal circulation, sug-

gesting that the fundamental mode of action of adrenin and ephedrine is quite different. (It is interesting in this connection to refer to a recent discussion of the action of ephedrine by Gaddum.[10]) Adrenin, as I have pointed out above, acts apparently exclusively upon the efferent glomerular arteriole. We have found no drug which acts exclusively upon the afferent arteriole, though there is evidence that afferent constriction plays an important part in reflexly elicited ischemia.

I turn now to experiments dealing with vasodilatation of the renal arterioles. Early in our investigations we sought some means of increasing the renal blood flow by vasodilatation and in the past three years we have expended an extravagant amount of time on this problem. May I remark in this connection that when the experimenter fails to accomplish a result which is rationally to be expected he is likely to be on the threshold of a new discovery, and further, that he frequently learns more from accidental adventures than from well planned experiments. That we can finally report a means of producing renal hyperemia in the human kidney involves, in a sense, a new discovery about that organ, and the discovery of the method of producing this hyperemia certainly rests upon a fortuitous circumstance.

Inulin, which we use for measuring the filtration rate, is physiologically inactive when properly prepared, as may be demonstrated by the absence of any disturbance in renal function, body temperature, blood pressure or subjective feeling, in subjects receiving intravenous infusions over periods of several hours. But early in our investigations we encountered difficulty in obtaining suitable inulin, inasmuch as some samples of it contain a powerful pyrogen, comparable to the pyrogen present in typhoid vaccine and probably com-

parable to the pryogen that too frequently invades intravenous infusions of saline, glucose, etc. We do not yet know the nature of this pyrogen, but its source may be the fragmented bodies of contaminating yeast, mould or bacterial cells which have grown upon the inulin during the process of manufacture.[25]

In any case, we soon discovered that whenever the pyrogenic reaction, which consists of headache, lumbar pain, nausea and ultimate fever, was encountered renal hyperemia invariably occurred. This fact led us to investigate the action

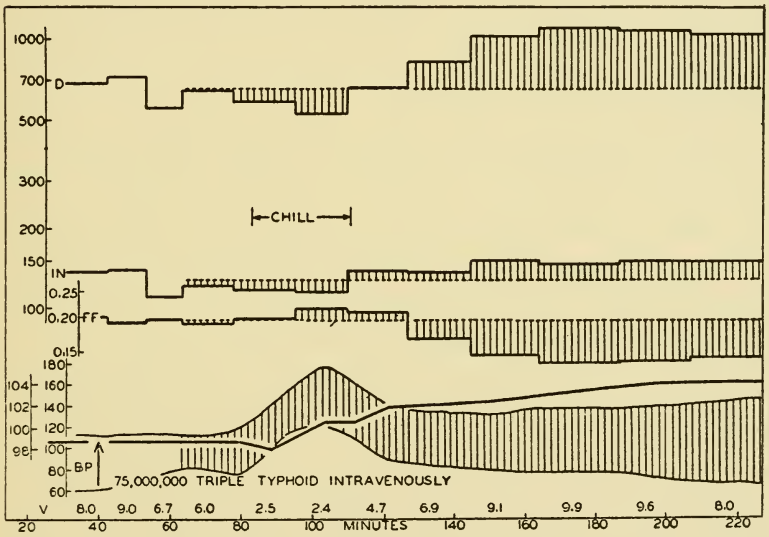

FIGURE 4

FIGURE 4. Illustrating the renal hyperemia produced by the pyrexial reaction. Legend as in Figure 1. (From 6).

of typhoid vaccine. As shown in Figure 4, after a short latent period, which serves as a control period, both diastolic and systolic pressure typically increase, this pressor phase usually coinciding with the febril chill. As the chill passes the blood

pressure falls, the diastolic usually falling below its control level, indicating that dilatation has occurred some place in the arteriolar bed. During the pressor phase the renal plasma flow may be substantially reduced, but during the subsequent phase of reduced diastolic pressure the renal plasma flow increases again and mounts to values substantially above the control level. This renal hyperemia is accompanied by a decreased filtration fraction, indicating that it is a result of dilation of the efferent glomerular arterioles. The change in filtration fraction is usually such as to just offset the increase in plasma flow, so that the filtration rate remains almost unchanged. Again, were one observing only the filtration rate it might be inferred, quite erroneously, that no change had taken place in renal function.

After examining the effects of typhoid vaccine, we turned to a particular sample of highly pyrogenic inulin (No. 268) as affording a superior method for producing renal hyperemia in man. This particular sample of inulin will produce a marked renal hyperemia in doses of 50 mgm. intravenously.* In thus turning evil to good account, we are utilizing the only method known to us for inducing renal hyperemia, for no drug which we have tried has this effect.

After adequate doses of pyrogen an increase in renal plasma flow of 50 to 75 per cent can be expected, though we have seen in a subject whose basal plasma flow averages 777 cc. per minute (=1204 cc. of whole blood), a hyperemia amounting to 1894 cc. of plasma (=3005 cc. of whole blood) per minute, an increase of 244 per cent.

*This inulin is of course thoroughly sterilized by boiling before administration. The pyrogenic activity of this particular sample is in striking contrast to the fact that when completely non-pyrogenic as much as 100 grams of inulin may be given without renal or systemic disturbance.

We have used the pyrogen method of producing renal hyperemia to examine the question of whether or not there are any inactive glomeruli or tubules in the normal or diseased kidney. Since the measurements of glucose-Tm and diodrast-Tm depend upon saturation methods, they are, as one might expect, very sensitive to temperature. Our available data indicate that the temperature coefficients of the reabsorptive and excretory processes in the tubules have a value of approximately 10 per cent per degree. It is desirable, therefore, to avoid any increase in body temperature during the measurement of glucose-Tm or diodrast-Tm, and this we have accomplished by the administration of amidopyrine prior to the administration of pyrogen. It is interesting that the amidopryine blocks not only the fever, but also the rise in blood pressure, the chill, nausea, and apparently most of the subjective symptoms, without blocking the renal hyperemia.

The action of adrenin and of pyrogen show that the renal blood flow can be decreased and increased through a considerable range of magnitude. It was our naive supposition that anesthetic section of the renal nerves would produce renal hyperemia by cutting off tonic vasoconstrictor impulses from the central nervous system. However, this expectation proved to be in error. In a recently completed series of investigations on normal subjects with high spinal anesthesia[28] it has been demonstrated that anesthesia adequate to block the reflex vasomotor responses has no significant effect upon the renal blood flow and we have concluded that when a subject is in the truly basal condition, i.e., horizontal and emotionally at ease, there are no tonic vasomotor impulses going to the kidney. The evidence points strongly to the conclusion that under these basal conditions the renal blood flow

is regulated entirely by the autonomous or local activity of the renal arterioles.*

We turn then to the demonstration that the renal arterioles are functionally connected with the nervous system. Elementary physiology teaches us that *Homo sapiens* pays a substantial price for his upright posture; every time he stands erect his blood tends to accumulate in the subcardial regions, particularly in the capillary and venous channels; he normally resists the venous failure which this stagnation favors by walking to and fro, the restless contractions of his leg muscles, aided by the venous valves, serving to promote the return of blood to the right heart. If, however, he stands still progressive venous stagnation leads to progressive decrease in cardiac output, which in turn tends to reduce arterial pressure; through the vaso-sensitive zones (aortic arch and carotid sinus) the first lowering of mean arterial pressure elicits reflex vasoconstriction throughout the body. In this response to posture we have an excellent means of evoking reflex excitation of the vasoconstrictor paths.

In the experiment shown in Figure 5 the subject, after three control periods in the horizontal position, stood upright, leaning against the wall until syncope occurred. This is not a very protracted ordeal, as most of those who have tried it can testify. As soon as he assumed the upright posture the renal plasma flow decreased; in view of the fact that the mean arterial pressure did not decrease, but was in fact slightly increased, this renal ischemia must be attributed to constriction of the renal arterioles. The fall in filtration fraction indicates that here constriction of the afferent arterioles

*This conclusion acquires special interest in view of recent anatomical studies of the glomerular apparatus which indicate the presence in both the afferent and efferent arterioles of a rather elaborate system of specialized myo-epithelioid cells the local responses of which may determine the caliber of these vessels (See 7).

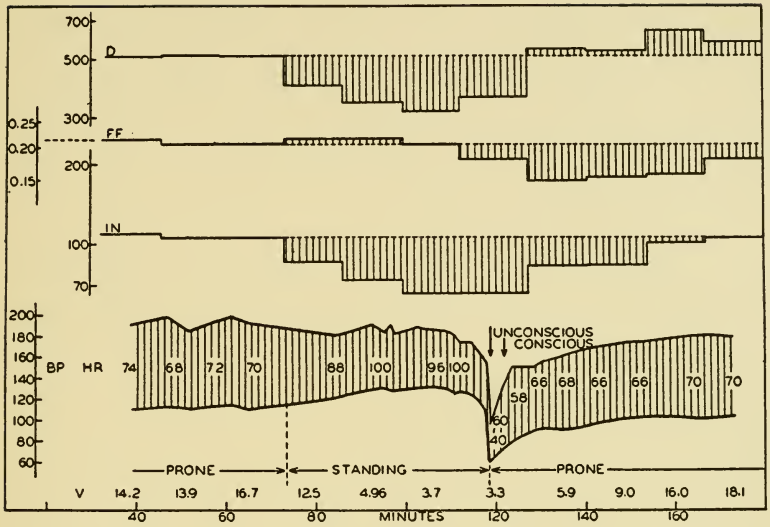

FIGURE 5

FIGURE 5. The effective renal plasma flow, etc., during syncope induced by the sustained upright posture in a hypertensive subject. Legend as in Figure 1. Note the slowing of the heart rate (HR) which accompanies the fall in blood pressure.

plays an important part. This experiment leaves us in no doubt as to the possibility of nervous vasoconstriction in the kidney, in spite of the primal autonomy of the renal circulation.

Again, I would like to comment in passing on a related aspect of this experiment. It is frequently stated that orthostatic syncope is caused by arteriolar dilatation following vasomotor failure. But you will notice that the blood pressure of the subject shown here gives no evidence of vasodilatation; rather he displays a picture of progressively decreasing venous return with consequent decreasing cardiac output, the arterioles seemingly remaining constricted to the end. Though we cannot assert that it is invariably true, syncope in this case was accompanied by a marked slowing of the heart,

and we suspect that it is this cardiac inhibition, presumably mediated through the vagus, which is immediately responsible for cerebral anoxia and loss of consciousness. The importance of cardiac inhibition in syncope has been pointed out by Sir Thomas Lewis,[17] but it has not received the attention which I believe it merits.

Returning to the kidney, I particularly call your attention to the fact that the subject of the above experiment had essential hypertension. I have exhibited a hypertensive subject rather than a normal one for deliberate reasons. Normal and hypertensive subjects behave very much alike; individuals in both groups show differences in sensitivity to venous failure, which makes it difficult to quantitate the local renal response. It is enough for the moment to be able to assert that when either the normal or the hypertensive subject assumes the upright, immobile posture the blood flow through the kidneys may be substantially reduced by reflex vasoconstriction.

Let us turn now to the question of what happens in the renal circulation during ischemia and hyperemia. The conventionally accepted description for the normal kidney is that essentially all the tubular capillaries are supplied from the efferent glomerular arterioles. If such is the case, constriction of either afferent or efferent arterioles would be expected to produce some tubular ischemia, even though the glomerular circulation were not completely arrested. But in the pathological kidney, according to Oliver,[21] direct connections exist between the arteriolar tree and the peritubular capillaries; functionally equivalent connections have been described in the normal kidney by Fuchs and Popper,[9] and Spanner[29] asserts that in the normal kidney there are numer-

ous anastomoses between the arterial tree and the venous circulation. Spanner believes that through these anastomoses a retrograde tubular circulation can be maintained quite apart from the glomerular circulation. In any of these instances, partial closure of the glomerular circulation might forcibly deflect blood through these extraglomerular channels and actually increase the peritubular blood flow. On the other hand, constriction of the direct arteriolar channels might induce some degree of glomerular hyperemia while producing tubular ischemia.

It is clear that one cannot *a priori* predict the effect of a constrictor agent upon the renal circulation. In inquiring into this question experimentally we have measured the number of active glomeruli by glucose-Tm, and the number of active tubules by diodrast-Tm. In an experiment already described (Figure 2), it was observed that adrenin did not appreciably change glucose-Tm, which is an index of the number of active glomeruli. In that experiment diodrast-Tm was omitted so that we could follow the renal plasma flow during the action of the hormone, since during the measurement of diodrast-Tm the tubules are saturated with diodrast and the diodrast clearance no longer reflects the renal plasma flow. Apart from this consideration it is possible to measure both glucose-Tm and diodrast-Tm at the same time; if one wishes to have a figure on the existing renal plasma flow, this must be measured in advance of diodrast-Tm.

Our usual method of examination is illustrated in Figure 6. This figure shows three groups of data: basal, during the action of adrenin, and during hyperemia. Each heavy, solid line represents the average of 4 or 5 clearance periods. In the first half of each experiment the subject was prepared for

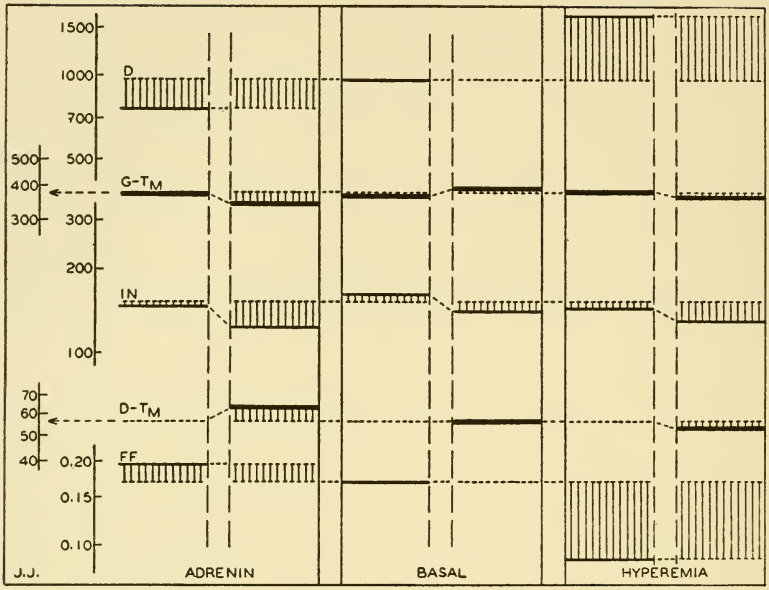

FIGURE 6

FIGURE 6. Method of examination of action of adrenin and hyperemia on renal function. Legend as in previous figures, except D-Tm, which indicates diodrast-Tm in mgm. of iodine per minute. D-Tm is the maximal rate of tubular excretion of diodrast under conditions of tubular saturation, and is a measure of the number of active, normal tubules in the kidney. Since the extraction ratio of diodrast is reduced during the measurement of D-Tm, the diodrast clearance (D) is no longer a measure of renal plasma flow, and this value, as well as the filtration fraction (FF) must be interpolated from the control observations at the left of each section.

the observation of diodrast and inulin clearances, and for glucose-Tm. After four clearance periods, the plasma diodrast level was raised to 40-60 mgm. per cent of diodrast iodine, and diodrast-Tm was measured during 5 clearance periods. The interval separating these two groups of observations need be no longer than 20 minutes, and the renal plasma flow as observed during the first half of the experiment may be assumed to indicate the plasma flow when diodrast-Tm is being measured.

Under adrenin the renal plasma flow in this subject was decreased from the basal value by 20 per cent, while during hyperemia the renal plasma flow was increased over the basal by 74 per cent. In spite of these marked changes glucose-Tm and diodrast-Tm showed only slight and perhaps insignificant changes.* The same may be said of other observations of this type on normal subjects. Our conclusions on this matter must be considered as tentative, but our results to date show that adrenin in substantial therapeutic doses does not close the glomeruli of the human kidney.† Under the action of this hormone there is a slight but consistent increase in diodrast-Tm, maximally about 15 per cent; if this is confirmed in further observations it suggests that during constriction of the glomerular arterioles blood may be deflected into peritubular capillaries in which the flow has previously been considerably below the average. During hyperemia, on the other hand, neither glucose-Tm nor diordast-Tm show changes beyond the limits of the possible error. These observations need to be expanded, and for the moment it is best simply to emphasize the smallness of the changes in any instance. As they stand the results indicate that all the glomeruli in the normal human kidney are active under basal conditions, in the sense that in no appreciable number is the rate of filtration substantially less than the average; and that nearly all the tubules are irrigated with an adequate supply of blood, in the sense

*The average rectal temperature under basal conditions is 98.5°F.; during the pyrogenic reaction, even after a prolonged course of amidopyrine, the temperature may rise 0.5 or 1 degree and this fact makes it necessary to apply a slight temperature correction. We need to know more about the actual value of this temperature correction than we do at the present time, but in this discussion the data are corrected on the assumption that both glucose-Tm and diodrast-Tm increase by 10 per cent for each degree of fever above 98.5°.

†It may be remarked, however, that perhaps we should not expect to close a glomerulus by constricting the efferent arteriole.

that in no appreciable number is the blood flow substantially below the average.*

Summarizing this portion of this paper, the picture which we have of the normal human kidney is an organ composed of a million-odd nephric units, each presumably capable of functioning more or less independently of the other, in which the blood flow, both glomerular and tubular, is determined by the autonomous activity of the glomerular apparatus or other local vascular devices; connection with the autonomic nervous system is unnecessary for the maintenance of local renal constrictor tone, and the autonomic nervous system contributes little if anything to the regulation of renal blood flow under basal, resting conditions. The two kidneys normally receive about one-third of the total cardiac output. The renal blood flow can be substantially reduced by adrenin and by reflex vasoconstriction, and it can be increased during the pyrexial reaction, the maximal renal blood flow being perhaps 100 per cent above the basal value. In spite of the fact that the basal renal blood flow is only about half of the apparent maximal value, it appears that all the glomeruli and tubules are active in the basal condition, in that the number of functioning units, either from the point

* In all our present observations the load of glucose and diodrast delivered to the tubules is considerably in excess of the minimal load required to effect saturation when the latter is evaluated in terms of the average filtration rate and plasma flow for all nephrons. By reducing the plasma levels of glucose and diodrast towards the critical levels slight variations in filtration rate and tubular blood flow would be revealed, but we have preferred in the first instance to work under conditions suitable for the detection of more marked ischemia. For a discussion of the quantitative limitations of these saturation methods the reader is referred to the footnote on page 32. The above results controvert the belief that perhaps as many as 40 per cent of the glomeruli in the human kidney are wholly or nearly active at any one moment. This belief had its origin in no experimental evidence, so far as man or mammals are concerned; but the organization of the frog kidney is in many respects very different from that of the human kidney, and the observation rests solely upon the fact that the frog kidney shows alternation of glomerular activity cannot be transferred from frog to man with any rational justification.

of view of glomerular filtration or tubular excretion, is not increased by hyperemia.

I turn now to a brief discussion of renal function in subjects with essential hypertension. Our investigations have been in progress for several years[13,27] and have been accompanied by a thorough clinical and X-ray study of the patients. Lack of space unfortunately precludes the inclusion of history, physical examination, etc. The diagnosis of essential hypertension has been based upon the usual clinical criteria, though a few subjects with history of renal lithiasis or infection have been included, but no subject is included who presented any history or signs suggestive of glomerulonephritis.

In the earlier period of this study we had not yet developed the methods for measuring glucose-Tm and diodrast-Tm, and consequently our information in this respect is not as complete as we would wish. However, we have sufficient information on these functions from our recent observations to justify a tentative discussion.

A summarizing chart, showing the more important data on renal function as found in 15 hypertensive subjects, is given in Figure 7. This chart includes only those subjects who show 30 per cent or better of renal parenchyma still intact. It is not implied that a seriatim comparison of various individuals in this manner depicts the course of hypertensive disease. It is simply a convenient physiological method of analysis. At the left of the figure there are given our standard normal values for the renal plasma flow, filtration rate, diodrast-Tm and filtration fraction.*

*The average normal value of diodrast-Tm is based on only 14 normal subjects, the other data on 34 normal subjects, some of whom have been examined repeatedly. These standard values are not final and will be amended as rapidly as our observations on normal subjects are expanded.

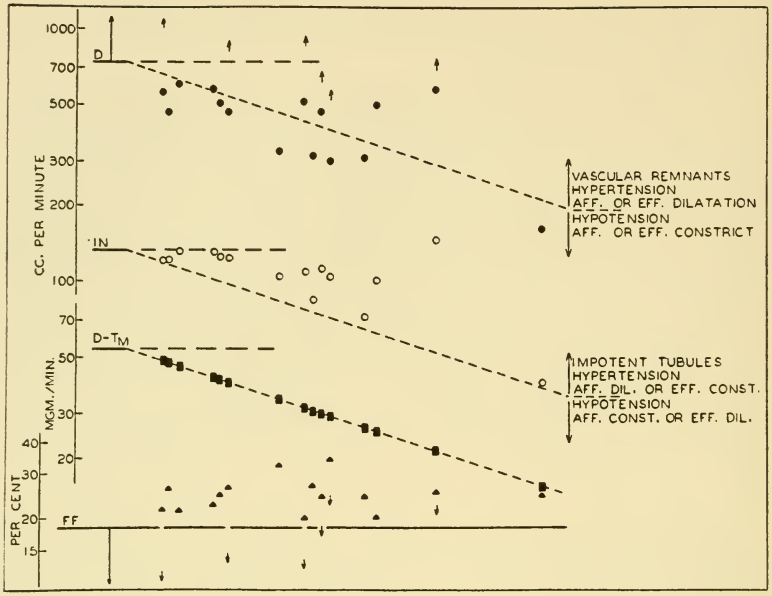

FIGURE 7

FIGURE 7. The effective renal plasma flow (D), filtration rate (IN), tubular excretory mass (D-Tm) and filtration fraction (FF) in 15 subjects with benign hypertension. The data are fully discussed in the text.

The first impressive fact in these data is that here is a disease which probably from its onset progressively destroys the renal parenchyma. Apart from advanced malignant nephrosclerosis it is impossible to predict from the usual clinical evidence or the patient's history whether the renal parenchyma will be found to be essentially intact or reduced to 50 to 40 per cent of its normal value. As yet in no individual with hypertension have we found diodrast-Tm equal to the average normal value, and in only the first three subjects at the left does it exceed the lowest observed normal value. Yet it is possible that these three subjects have suffered some pathological reduction in tubular excretory mass.

Secondly, in no single individual have we ever found a

renal plasma flow equal to the average normal value, and in only three subjects (the 1st, 3rd, and 4th) does it exceed the smallest observed normal value. In the absolute sense all subjects show renal ischemia.

In considering what plasma flow is to be expected in any subject, it will be readily agreed that it is misleading to consider the absolute renal plasma flow in a disease which is progressively destroying renal tissue; if 50 per cent of the kidney were destroyed we would expect the plasma flow to be reduced proportionally, or roughly so; and if the remaining 50 per cent had a normal plasma flow per unit of intact tissue we would, from the experience of unilateral nephrectomy, expect this plasma flow to be physiologically adequate. It is obviously more appropriate in a problem such as this to consider not the absolute value of the renal plasma flow but the plasma flow per unit of residual, functionally intact tissue.

We may take diodrast-Tm, which reflects the quantity of intact tubular tissue, as a basis of comparison, and relate these subjects to each other and to the normal according to the magnitude of this value. To facilitate this comparison graphically we have simply drawn three parallel sloping lines from the normal values of renal plasma flow, filtration rate and diodrast-Tm at an arbitrary but convenient angle, and then arranged the subjects in order of decreasing diodrast-Tm. Since these data are plotted logarithmically, this arrangement is such that if one were to reduce all functions in the normal kidney progressively and in a proportional manner, these functions would decrease along these parallel lines. Another advantage of using logarithmic ordinates is that equal linear excursions up or down in any variable represent equal percentual changes.

If the renal plasma flow were reduced *pari passu* with the renal parenchyma, as measured by diodrast-Tm, this plasma flow would descend along the upper line. This is roughly the case, but most of the subjects show a plasma flow per unit of residual functional tissue which is markedly below the expected value. These subjects may be said to show a relative or functional ischemia of the residual excretory tissue. The frequency of this functional ischemia suggests that the renal vascular bed is being occluded in advance of the destruction of renal parenchyma, rather than that the progressive destruction of both vascular bed and parenchyma are proceeding simultaneously.

The interpretation of the course of events in the hypertensive kidney presents many complexities and must proceed cautiously; the data in Figure 7 appear at first sight to present several contradictions, and in any case the measurement of the total plasma flow, total filtration rate and total excretory mass does not immediately throw light upon what is going on in individual nephrons. But when we consider these data in terms of the possible courses of events there emerge several impressive consistencies. In the interests of brevity we may attempt a further analysis of the data by hypothesis, and by observing wherein these data are consistent with this hypothesis.

But first let us note what factors could in principle modify the plasma flow and filtration rate. On the one hand, the plasma flow would tend to be decreased by systemic hypotension, or by constriction of either the afferent or efferent arterioles. (Any arterial occlusion on the afferent side of the glomeruli may be included in afferent constriction.) On the other hand, the renal plasma flow would tend to be in-

creased by systemic hypertension and by arteriolar dilatation. And where part of the renal parenchyma has been destroyed, vascular remnants might persist which, within a certain radius of diffusion, could irrigate the nearby residual functional tissue and thus produce to all intents and purposes a hyperemia in that tissue. We would expect such vascular remnants to persist where there were being formed what we have previously called impotent tubules, i.e., tubules which have lost their excretory capacity but which remain connected with intact, functioning glomeruli.

The factors enumerated above would also tend to elevate the filtration rate, except that here we must distinguish between constriction of the afferent and efferent arterioles, which in principle will have opposing effects upon the filtration pressure.

Now hypotension is clearly ruled out of this problem as a cause of renal ischemia, and we are left with a choice between afferent and efferent arteriolar constriction. Let us take as our assumption the premise that the locus of the constriction is at the efferent arterioles and see to what extent the facts are consonant with it. Efferent arteriolar constriction will lead to renal ischemia, as for example, under the action of adrenin, but because of the maintained or even increased filtration pressure which occurs when the constriction is on the far side of the filtering bed, the filtration rate will not decrease in a parallel manner but will tend to be maintained in spite of this ischemia. Offsetting the tendency of the vascular constriction to produce ischemia will be the systemic hypertension which is characteristic of the disease; and, where destruction of renal parenchyma has occurred, vascular remnants persisting around defunct tubules may

greatly increase the blood available to the intact tubules and thus produce an apparent hyperemia of the residual functional tissue. The hypertensive subject, while usually showing a relative ischemia, shows an essentially normal filtration rate; these two facts are therefore consonant with the hypothesis of efferent arteriolar spasm. Also contributing to the maintenance of the filtration rate, of course, is such systemic hypertension as exists and, what is perhaps more important, the presence of impotent tubules. The fact that some subjects in whom extensive destruction of renal parenchyma has occurred show a relative hyperemia may be attributed to vascular remnants without contradicting the assumption that vascular constriction is the primary perturbation.

In consequence of the maintenance of filtration rate in the face of decreased plasma flow, the filtration fraction is substantially increased. In not a single hypertensive subject examined by us has the filtration fraction been down to the normal value. If the vascoconstriction responsible for the ischemia were on the afferent side of the glomeruli, one would expect to find the filtration fraction below normal in some instances at least, particularly those where the renal parenchyma is only slightly injured. Failure to do so is strong evidence of efferent spasm.

We may next inquire, is this efferent spasm amenable to physiological reversal, or does it have the nature of a rigid, irreversible occlusion? Information can be obtained on this question by observing the response during the pyrexial reaction, which in the normal kidney produces a substantial hyperemia. Not all subjects studied by us have been examined in this manner, but those who have been examined have invariably shown a hyperemia of some degree, as shown

by the arrows in the chart. In some instances the maximal observed blood flow is of the order of magnitude to be expected in the normal kidney, so we may infer that in great measure, at least, the obstruction is functionally reversible.

During hyperemia the filtration fraction in the hypertensive kidney never increases, as would be expected in principle were the obstruction on the afferent side of the glomeruli, but it invariably decreases, as shown by the arrows at the bottom of the chart. Again, this fact points to efferent constriction. The fact that the filtration fraction does not fall as low as in the normal kidney may be attributed to systemic hypertension or more probably to the presence of impotent tubules.

We have examined the effects of hyperemia on glucose-Tm and diodrast-Tm in only a few of these subjects. In most instances the changes are slight and perhaps not beyond the experimental error, and in no instance as yet have we found evidence that hyperemia opens any inactive glomeruli in the hypertensive kidney. However, in one subject (the next to last on the right in the chart) diodrast-Tm was increased during hyperemia to the remarkable extent of 94 per cent, which means that the quantity of tubular tissue reached by blood was increased during hyperemia to this extent. The simultaneous increase in glucose-Tm was only 6 per cent, indicating that the ischemic tissue which was opened to circulation by hyperemia was predominantly tubular in nature.

Summarizing these functional studies, the picture we obtain of the hypertensive kidney is that in this disease there is early and progressive loss of tubular function, as revealed by reduction in the tubular excretory mass (diodrast-Tm). The presence and extent of the destructive process is not re-

vealed, at least in the milder forms of hypertension, by any reduction in the rate of glomerular filtration, which is maintained for possibly three reasons, efferent arteriolar constriction, the formation of impotent tubules and systemic hypertension. There is invariably an ischemia, in terms of absolute blood flow; and usually there is a relative ischemia of the residual functional tissue, though the presence of vascular remnants and perhaps the effect of systemic hypertension may in some instances have the effect of producing a relative hyperemia of the residual functional tissue.

The frequency with which ischemia relative to the residual functional tissue occurs in these subjects suggests that there exists a perturbation of vascular function which is primary in time and causality to the destruction of renal parenchyma, i.e., that the destruction of renal parenchyma is a result rather than a cause of the ischemia. The major facts can be explained on the assumption that the immediate perturbation of function is an excessive constriction of the efferent glomerular arterioles, which is in great measure at least functionally reversible under conditions which produce hyperemia in the normal kidney. The cause of this constriction is, however, undetermined; it may be due simply to the presence in the systemic circulation of a vasoconstrictor principle which is acting upon the arterioles of the body generally, or it may be a physiological response secondary to occlusion on the afferent side of the glomeruli.

Neurogenic vasoconstrictor activity, which is elicited by the sustained upright posture and which can produce ischemia in the normal kidney, can aggravate the existant ischemia of the hypertensive kidney. This fact demonstrates the possibility of a neural contribution to the disturbed renal func-

tion, particularly under circulatory stress, but it does not demonstrate that the vasomotor paths are involved in the causation of the ischemia under basal conditions. Under basal conditions the renal vasomotor paths are normally inactive, and the determination of whether or not this is true of the hypertensive kidney must await further examination.

The evidence clearly indicates the presence in the hypertensive kidney of impotent tubules, in addition to the indubitable tubular fragments and scar tissue which result from the destructive process of the disease. Presumably having a good blood supply, these impotent tubules, along with scar tissue and tubular fragments, afford an opportunity for the absorption into the systemic circulation of physiologically active substances.

On the question of the extent to which hyperemia will restore circulation to such ischemic tissue as is still capable of functioning we would at this time venture only a tentative opinion. Under otherwise basal conditions, some hypertensive subjects have failed to show an increase in tubular excretory mass during hyperemia, while in others an increase occurs, one subject showing an increase of functional parenchyma of nearly 100 per cent. But in this connection we must ask, How long can tubular tissue tolerate ischemia and yet retain instantaneously reversible, functional capacities? And can we expect to discover ischemic but potentially functional tissue in every instance, and particularly in the resting quasi-basal conditions under which these observations have been made? It may be that significant reversible ischemia would be observed only under conditions of circulatory stress (fatigue, exercise, venous inadequacy, etc.) The answer to the two questions posed above may throw more light on the

etiology of hypertension, or at least on the course of renal injury, than can the mere demonstration of the existence of ischemia *per se*.

In the ordinary course of events it would be encumbent upon me to relate the above facts to our rapidly expanding knowledge of the pathology of hypertension, and particularly to the demonstration by Goldblatt and his collaborators, and by numerous other investigators, that hypertension can be produced in animals by moderate renal ischemia, and that this hypertension is caused by a substance which is absorbed into the blood from the ischemic renal tissue and which mediately or immediately evokes generalized vasoconstriction. This work has, however, been so frequently reviewed that repetition seems superfluous.[3,11,12,14,15,18,24,31] Rather may I be allowed to relate this discovery to our own investigations, and, speaking as a physiologist, comment upon the broader implications of this problem.

That the Goldblatt principle plays a primary, causal role in some forms of human hypertension is very definitely indicated by the demonstration that all signs of the disease are in some instances obliterated by the removal of a single diseased kidney or by the surgical correction of locally impaired renal function.[2,4,5,8,16] Consequently the process of excluding known specific pathology of the kidneys in order to arrive at a residual entity which may be called "essential hypertension," in that it has no demonstrable renal basis, is perhaps akin to what the biologist calls "species splitting", and too much ardor in this direction may lead us into as much error as would the careless neglect of specific renal impairment (See 23). The present demonstration that hypertensive disease, when unaccompanied by specific renal pathology,

is typically characterized by renal ischemia and impairment of tubular function· leaves less reason than ever to divide renal and essential hypertension into two entirely independent categories. It would be easy to jump to the conclusion that the kidneys are the primary locus of pathology in every case, and to believe that renal ischemia, by initiating tubular injury, accelerated the formation or absorption of the Goldblatt hypertensive principle which, by reacting on the renal arterioles, induced further constriction in the renal vascular bed and thus contributed to a gradual but vicious cycle of ischemic renal destruction.

But before accepting this conclusion, we must note that the Goldblatt principle has not as yet been shown to produce in the human kidney the specific circulatory disturbance which is characteristic of the disease; neither has it as yet been demonstrated that the Goldblatt principle, when allowed to act over a long period of time, can produce the destructive changes which are observed in the disease; nor can it be explained, without invoking too much hypothesis at the present time, how the primary renal ischemia is initiated. If we are to attach little or no significance to these gaps in the logical chain· then tremendous responsibility must devolve upon the kidneys, a responsibility which I cannot describe better than by quoting from the pathologist, Jean Oliver,[20] who in discussing the so-called "normal" senescence of man, says:

"As a part of the senescent process there develops a generalized sclerosis of the smaller arteries. Other factors fortuitous or 'pathological' may influence the course of the vascular alteration, but with this we are not at present concerned. The vascular change within the various tissues and organs may be severe, but there is no evidence that compels

the conclusion that these lesions produce an elevation of blood pressure. If the arterial change within the kidney is sufficient to produce renal ischemia, however, hypertension follows. Depending on the degree of renal arterial involvement the hypertension may be 'benign' and senility ends with mild circulatory difficulties and a beneficient broncho-pneumonia; more grave, and cardiac failure or cerebral accident, depending on the condition of the local vessels, terminates in more dramatic fashion life's last episode.

"By such a concept it is not so much vascular senescence, common to all organs and tissues, that determines the ultimate outcome, but a disturbance within the kidney and peculiar to its functions that is the final and actuating mechanism of senile circulatory failure and accident.

"A man's arteries may then be old, but only if his kidneys are spared does his senescence approach the biological ideal of a gradual and peaceful decline."

This attractive view is, however, complicated by the possibility that arteriolar sclerosis may itself be a result of prolonged hypertension rather than an initiating cause of the disease.[11,12]

To read the rapidly expanding literature on this subject is only to discover the complexity of the problem of ultimate etiology. One observer holds that hypertension is of dietary origin, while another relates it to climate, both interpretations being far from negligible since the incidence of the disease is remarkably low among many primitive peoples. By other observers it is contended that there is a distinct hereditary trend, at least in predisposition, while correlations with endocrine imbalance, particularly of the gonads, are not lacking. At the other extreme, the psychoanalysts tell us that

the early fluctuating phase of essential hypertension is a manifestation of a psychoneurosis based on excessive and inhibited hostile impulses;[1] and again, that inhibition of heterosexuality or repression by a dominant mother, with chronic hostile but unsuccessful rebellion against submissiveness, are common psychological features of the disease.[22]

Therapy is frequently a guide to etiology; and we may note that high blood pressure (and too frequently only high blood pressure) has been optimistically treated by herbals, a diet poor in meat or poor in salt, by extraction of teeth or tonsils, by high colonic irrigation, by abstinence from alcohol, tobacco, coffee and tea, by systematic relaxation, by injection of various endocrines, by excision of part or nearly all of the autonomic nervous system, by a variety of drugs (with usually no knowledge whether these drugs act upon the heart, the arterial or the venous circulation), and last but not least in efficacy, by simple suggestion. One should not too quickly deprecate any of these efforts: rational medicine has ample reason to respect quasi-empirical therapy after some recent experiences. And as a physiologist having no therapeutic axe of my own to grind, I am not concerned whether the herbalist, the surgeon or the psychoanalyst comes out first in this therapeutic competition, though I am, of course, delighted that each one has achieved a modicum of success.

In the present state of our knowledge, it would be hazardous to advance the kidney as more than one contributor to a malignant *melange* which, if we are to accept a fraction of the evidence, is a constitutional disorder involving in addition to the kidneys, the vascular bed, the vasomotor centers, the cerebral cortex, perhaps the entire organism and its genetic foundations. And yet, considering the tentative na-

ture of most of the suggestions which have been made in regard to etiology, it is unnecessary to magnify them. It is definitely demonstrated that hypertensive disease can be produced by renal ischemia in animals where the biotic complex does not contain repression psychoses, psychic trauma or genetic predisposition; there is good evidence that disturbed renal function is in some instances the cause of hypertension in man; and our present evidence shows that in all hypertensive subjects so far examined renal function is disturbed in some degree, sometimes only slightly and sometimes markedly, but always in the qualitative direction to be anticipated if renal ischemia is in any way important. Whether this renal ischemia is cause or effect and, if it is a cause, how the ischemia itself is initiated, are questions that remain for further examination.

When and if it can be demonstrated that the relief of renal ischemia specifically abolishes all signs of hypertensive disease in man, then the major link in the chain of logic which incriminates the kidneys will be complete. This is asking that we reach our *desideratio summa,* the cure or prevention of the disease, at the beginning of our problem, which is perhaps more than we can expect, but short of this demonstration it is impossible to charge the kidneys with sole responsibility.

Since, however, the evidence pointing to the importance of renal ischemia is so strong, it would seem the course of wisdom to start from this point and, joining forces with the surgeon, the neurologist and the psychoanalyst, to work backwards, as it were, through the maze of environmental, psychological and hereditary factors in our efforts to discover such other causes as may be operative, and to relate the renal ischemia to the organism as a whole.

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